The Effect of Increased PET Imaging on the Staging, Outcomes, and Health Care Utilization of Medicare Non-Small Cell Lung Cancer Patients

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ABSTRACT

MICHAELA A. DINAN: The Effect of Increased PET Imaging on the Staging, Outcomes, and Health Care Utilization of Medicare Non-Small Cell Lung Cancer Patients
(Under the direction of Morris Weinberger, PhD)

Positron Emission Tomography (PET) is an advanced imaging modality that was first approved by Medicare in 1998 to differentiate between malignant and benign solitary pulmonary nodules. It has since has experienced rapid uptake in clinical practice among both Medicare and privately-insured non-small cell lung cancer (NSCLC) patients, despite a lack of large randomized trials examining how the use of PET affects NSCLC patient outcomes. The three studies in this dissertation used Surveillance Epidemiology and End Results (SEER)-Medicare data from 1992 to 2005 to examine how the widespread adoption of PET has affected the evaluation, staging, treatment, and health care utilization of Medicare beneficiaries with NSCLC.

By 2005, more than half of all NSCLC patients received one or more PET scans. Despite widespread adoption of PET overall, differential rates of PET utilization within sociodemographic and regional subgroups persisted through 2005, with lower rates of PET use observed among blacks, patients older than age 80, and patients living outside the Northeast. Widespread adoption of PET was accompanied by an increase in the proportion of cancers staged as unresectable, reduced rates of lung resection, and decreased inpatient health care expenditures by 2005. During the same period, the proportion of patients

undergoing chemotherapy increased, resulting in an overall increase in expenditures for Medicare beneficiaries with NSCLC.

The widespread use of PET among the Medicare NSCLC occurred non-uniformly, induced stage migration, changed patient treatment and costs, but did not improve overall survival. In the era of individualized medicine, the role of PET may shift from an initial diagnosis and staging modality to a role in treatment evaluation. The increased use of PET in the Medicare NSCLC patient population and how it affects patient management and health care utilization remains an important area of ongoing research and evolving health policy.

In memory of John J. Dinan.

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PREFACE

Consistent with the 3-paper option for a dissertation, the first chapter provides the introduction and specific aims of the dissertation. Chapter 2 gives a background literature review, Chapter 3 presents the conceptual model for the research, along with the research questions and hypotheses. Chapter 4 describes the methodology used for the three studies in this dissertation. Chapters 5, 6 and 7 are the three individual manuscripts; because they are to be submitted for publication, there are some redundancies across papers. Chapter 8 presents a summary of the findings, policy implications, strengths and limitations of the three studies and provides directions for future research.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ACRONYMS AND ABBREVIATIONS

AJCC	American Joint Committee on Cancer
CMS	Centers for Medicare & Medicaid Services
CAT	Computerized Axial Tomography
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cerebrovascular Disease (stroke)
CT	Computed Tomography
CPT	Current Procedural Terminology
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FNA	Fine Needle Aspiration
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDC	National Drug Code
NSCLC	Non-Small Cell Lung Cancer
PET	Positron Emission Tomography
PVD	Peripheral Vascular Disease
SCLC	Small Cell Lung Cancer

SEER	Surveillance, Epidemiology, and End Results
SEER SS	SEER summary
SEER EOD	SEER extent of disease
SPN	Solitary Pulmonary Nodules
TNM	Tumor, Node, Metastasis

CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

Positron Emission Tomography (PET) is an advanced imaging modality that was first used to differentiate between malignant and benign solitary pulmonary nodules in 1992[1]; it was initially approved for this use by Medicare in 1998[2]. Since then, PET usage has experienced rapid uptake in clinical practice among both Medicare and privately-insured non-small cell lung cancer patients.[3,4] By 2005, more than a third of Medicare lung cancer beneficiaries were receiving one or more PET scans. To date, randomized controlled trials (RCTs) investigating the effect of PET on NSCLC have not been adequately powered to detect a survival advantage. [5-8] Initial epidemiologic analyses of Medicare lung cancer patients[9] and one large private California insurer [4] have reported that PET usage is associated with significant improvements in patient outcomes.

The association between PET use and patient outcomes is difficult to interpret because of strong patient selection biases, with PET being more likely administered to educated, higher income, white, married patients with early stage tumors [4, 9]. In addition, the preferential administration of PET in populations with greater access to health care may bias observed associations between PET use and positive outcomes. Moreover, because PET scan is a more sensitive detection method, it may result in higher tumor stages being given to biologically equivalent cancers, known as stage migration. A known effect of stage migration is that stage-specific survival outcomes may appear improved in the absence of any actual patient benefit. Studies outside the Medicare population have suggested that increased PET use may result in

stage migration;[6,10,11] however, this phenomenon has not been studied within the Medicare lung cancer population. Fully understanding the utilization of PET and how it affects staging, management, outcomes, and health care spending in lung cancer patients has considerable implications for the establishment of future imaging guidelines.

Thus, my dissertation, which will study the Medicare lung cancer patient population, has three specific aims:

Specific Aim 1: Characterize the dissemination pattern of PET from 1998-2005

A) Assess the association between race, sex, and age and PET use over time

B) Model the likelihood that an individual will receive PET over time

Specific Aim 2: Determine the presence and magnitude of PET-induced stage migration and the indirect association of PET use on patient outcomes from 1993-2005

A) Determine whether stage migration has occurred over time following the introduction of PET in:

i) the overall Medicare lung cancer patient population

ii) subpopulations within Medicare with differential adoption of PET

B) Estimate the magnitude of PET-associated stage migration

C) Investigate the indirect effect of PET on lung cancer outcomes over time, controlling for PET-induced stage migration

Specific Aim 3: Investigate the association of increased PET usage with lung cancer patient health care utilization within the Medicare population

A) Examine whether individuals undergoing PET vs. those not undergoing PET exhibit differential use of surgical and non-surgical treatment

B) Compare changes in surgery rates and health care costs as a function of time following the introduction of PET

The three aims in this dissertation examine how the widespread adoption of PET has affected the evaluation, staging, treatment, and health care utilization of Medicare beneficiaries with NSCLC. The first study will characterize which NSCLC beneficiaries received PET within the Medicare NSCLC patient population between 1998 and 2005 to assess potential selection bias and other factors associated with PET use from an epidemiologic perspective. The second study will examine stage migration and survival associated with PET adoption, exploring previous claims by others that PET was associated with improved survival. The third study will examine how PET affected the treatment and health care costs of NSCLC beneficiaries. By completing these aims, I hope to provide a rigorous characterization and assessment of the use and value of PET within the Medicare lung cancer population that can be used to effectively inform future health policy.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview

Cancer is a prevalent condition that accounts for significant morbidity, mortality, and healthcare expenditures in the United States. It is the second leading cause of death in the United States, and recently surpassed heart disease as the leading cause of death in Americans younger than 85 [12]. In 2008 alone, cancer claimed more than half a million lives and cost $228.1 billion, including $93.2 billion in direct medical costs [13]. Both the number of Americans affected by cancer and the cost of treating cancer have continued to increase in recent years. Individual cancer treatment costs in the United States have increased markedly, with the majority of emerging cancer chemotherapeutic agents costing more than $5,000 per month of treatment [14]. Emerging technologies such as imaging, robotics, and radiation therapy are estimated to be responsible for half of the growth in cancer-related healthcare expenditures[15-17]. Cancer-related expenditures in the United States are expected to grow faster than any other area of healthcare expenditures [18]. The majority of cancer patients are insured by Medicare, the policies of which not only directly affect health expenditures of Medicare cancer beneficiaries, but also influence coverage policies of private insurers and Medicaid programs.[19,20]

Lung cancer is the second most common cancer in both men and women, affecting approximately 1 of 14 individuals during the course of their lifetime.[13] It is also the leading cause of cancer-related deaths in the United States. The American Cancer Society estimated that there were 215,000 incident cases and 162,00 deaths from lung cancer in the U.S. in 2008[13].

Death from lung cancer can occur due to compromised lung function, opportunistic infections following partial lung obstruction, dehydration, malnutrition, or spread to other vital organs such as the brain, adrenal glands, liver, or bone. Smoking cigarettes is responsible for 80-90% of all lung cancers. Other risk factors include second hand exposure to cigarette smoke, asbestos fibers, radon gas, familial predisposition, lung disease, a prior history of lung cancer, and air pollution. Old age is also strongly associated with lung cancer, with 70% of people diagnosed after age 65 [13].

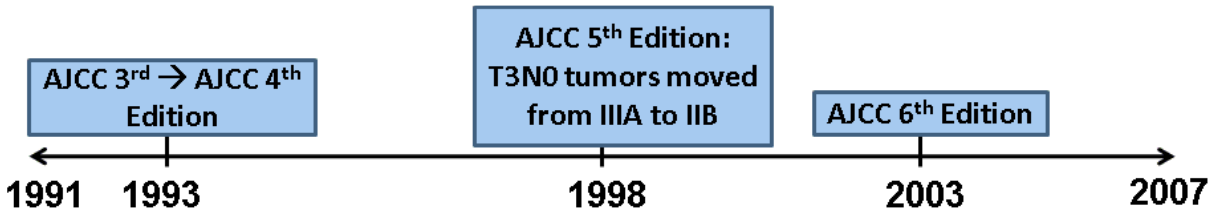
There are two types of lung cancer: small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). Staging, prognosis, and treatment for these two subtypes differ substantially [21]. About 20% of lung cancers are classified as SCLC, which is more aggressive and typically limited to smokers. The remaining 80% of lung cancers are NSCLC [13]. Due to the disparate nature of evaluation, staging, treatment, and prognosis of these two lung cancer subtypes, this study will only examine NSCLC.

2.2 Staging Systems of Lung Cancer

Physicians, epidemiologists, and public health proponents have found it useful to categorize the spread or aggressiveness of a cancer into discrete stages that reflect treatment and prognosis. Staging was first introduced by the World Health Organization in 1929 to categorize cervical cancer into four discrete stages [22]. The use of cancer staging has spread and evolved subsequently to meet the needs of organizations developing different staging systems for different purposes. Three major staging systems predominate in most tumor registries: 1) American Joint Committee on Cancer (AJCC or Tumor, Node, Metastasis (TNM)), 2) Surveillance, Epidemiology, and End Results (SEER) summary (SEER SS), and 3) SEER extent

of disease (SEER EOD) [23]. Neither the SEER EOD nor SEER SS systems are used clinically, but instead are designed to provide historically stable staging definitions to promote robust longitudinal epidemiologic studies of cancer. Instead, the AJCC system, also referred to as the Tumor, Node, Metastasis (TNM) system, is used by physicians to guide patient management and treatment and to provide information to patients regarding prognosis. The AJCC published the first edition of the *Manual for Staging of Cancer* in 1977, and has published an updated edition roughly every five years since then to keep up with the needs of physicians and evolving clinical guidelines (**Figure 2.1**). Although the exact details of the AJCC system have evolved with each new edition, its basic application over time has remained the same.

Figure 2.1: Timeline of Changes in NSCLC staging system



The AJCC TNM classification scheme is applied as the first clinical activity in caring for a patient with known or presumed lung cancer because this classification determines appropriate therapies [24]. This initial clinical staging occurs prior to any surgery or biopsies[21] and uses many of the procedures used to diagnosis lung cancer including standard chest X-ray, computed tomography (CT) scans, spiral CT, magnetic resonance imaging (MRI), positron emission tomography (PET), bone scans, and bronchoscopy. In addition, surgery or biopsies are used to gather data on tumor size and pathology, which can more accurately stage the tumor and, therefore, determine patient prognosis [1,21].

The most recent edition of the AJCC system used by SEER stages a patient's cancer using information about the primary tumor (T), spread to local lymph nodes (N), and the presence of metastases (M). Tumors are scored as follows: Primary tumors are given a "TX" for primary tumors that cannot be directly assessed, "T0" indicates no evidence of primary tumor, "Tis" indicates carcinoma in situ, "T1" is less than 3 cm and has not invaded the main bronchus, "T2" is larger than 3 cm or involves the main bronchus, "T3" directly invades the chest wall, diaphragm, or some surrounding tissues, and "T4" if the tumor invades the trachea, heart, large vessels, or esophagus. Lymph nodes are similarly given a "NX" if local lymph nodes cannot be assessed, "N0" if there are no regional lymph node metastases, "N1" if there is local spread to lymph nodes on the same side of the body as the primary tumor, "N2" if this spread reaches the area around the heart, and "N3" if lymph nodes on the opposite side of the body or more distant lymph nodes are affected. Metastasis is assigned an "MX" if distant metastasis cannot be assessed, "M0" if there are no distant metastases, and "M1 if there are distant metastases. This information is used to assign a categorical stage ranging from Stage I-IV (**Table 2.1**).

Table 2.1: TNM NSCLC stage

STAGE	TUMOR (T)	LYMPH NODE (N)	METASTASIS (M)
Occult Carcinoma	**TX**	**N0**	**M0**
Stage 0	**Tis**	**N0**	**M0**
Stage IA	**T1**	**N0**	**M0**
Stage IB	**T2**	**N0**	**M0**
Stage IIA	**T1**	**N1**	**M0**
Stage IIB	**T2**	**N1**	**M0**
	T3	**N0**	**M0**
Stage IIIA	**T1**	**N2**	**M0**
	T2	**N2**	**M0**
	T3	**N1**	**M0**
	T3	**N2**	**M0**
Stage IIIB	**Any T**	**N3**	**M0**
	T4	**Any N**	**M0**
Stage IV	**Any T**	**Any N**	**M1**

Source: AJCC staging manual, 6th edition

Over the time period relevant to this proposal, four AJCC editions have been in effect (**Figure 2.1**), however only the 3rd and 6th edition have been used by the SEER registry that was used in this research. Staging from the 3rd edition was provided by SEER prior to the beginning of the proposed study period in 1993, and was used until 2003. In 2003, SEER began using the 6th edition staging system. Beginning in 2003, stage I was split into stage IA and IB and stage II was split into stage IIA and IIB. In addition, T3N0 tumors were reclassified from stage IIIA to stage IIB. As a result, from 2002 to 2003 there may have been a small increase in the proportion of tumors staged as II and a decrease in the proportion of tumors staged as III.

2.3 Treatment of Lung Cancer

The National Cancer Institute (NCI) and the National Comprehensive Cancer Network (NCCN) are two of the leading organizations that provide guidelines for providers and patients regarding the appropriate treatment of cancers [25]. Based on stage, lung cancer treatment options include surgery, radiation, and/or chemotherapy (includes biologics). For cancers that have spread only locally, surgical removal of the cancer is the principal treatment modality. For patients whose disease has spread to distant locations in the body, referred to as metastatic or stage IV disease, surgery is generally not an effective treatment[25]. Stage IIIB is treated in the same manner as stage IV disease. Current NCCN guidelines recommend chemotherapy or targeted biologic therapy for patients with metastatic or recurrent disease[26]. Regardless of whether or not surgery is performed, chemotherapy and radiation can be used depending on the patient's health and cancer stage [25]. Higher stages indicate more aggressive cancer and are associated with reduced survival time and overall reduced survival.[27]

Stage I tumors (IA & IB) are generally treated by local resection (i.e. surgical removal of the tumor). For individuals who cannot undergo surgery due to poor health or advanced age, curative radiation therapy can be used instead. NCCN guidelines recommend chemotherapy for only a subset of stage I tumors, for example those with positive margins (leftover residual tumor) following resection [26]. Stage IA tumors are the least aggressive, and have an estimated 5-year survival of 75% in the United States, whereas stage IB tumors have a 5-year survival of 55%. Stage II tumors (IIA & IIB) have 5-year survival rates of 40-50% and are treated by local resection or curative radiation, but may benefit from adjuvant (additional) chemotherapy following surgical resection. Adjuvant radiation therapy is being explored in these patients in the setting of clinical trials [25].

Stage IIIA tumors may be treated by surgery, chemotherapy, and radiation. Individuals with these tumors have an overall poor prognosis with a 5-year survival ranging from 10% to 35%. Once the tumor has advanced to stage IIIB, however, patients no longer benefit from surgery. Instead, they may receive chemotherapy and radiation. Stage IV patients have metastatic disease. Again, surgery and radiation are not effective treatments, because they will only act locally. However, stage IV patients may still be treated using chemotherapy. Palliative radiotherapy can be used to provide relief from symptomatic primary or metastatic tumor sites. Patients with stage IIIB and IV have 5-year survival rates of 5% or less with most patients dying within a year of diagnosis [25].

2.4 Conventional Evaluation of Lung Cancer

Approximately 25% of people discover lung cancer during routine chest X-ray or CT scans, and may have no symptoms at the time of diagnosis [25]. The remaining cases are

diagnosed by symptoms caused by their cancer. Symptoms can result from the local presence of a tumor within the lung, from distant metastases, from hormones produced by the tumor, or indirectly via non-specific symptoms common to many cancers. Local spread within the lungs can cause difficulty breathing, wheezing, chest pain, coughing up blood, trouble swallowing, or local collapse and infection of the lungs. Distant metastases in the brain can cause neurologic symptoms such as headaches, seizures, stroke, or loss of motor control. Hormones or substances that act like hormones can be produced by lung tumors, which can cause systemic hormone and blood calcium imbalances. Nonspecific symptoms of any cancer including lung can include fever, weight loss, weakness, fatigue, and depression [25]. All putative diagnoses of lung cancer must be confirmed by the presence of malignant cells by a pathologist. Physical samples of tumor cells can be obtained directly from the tumor itself by bronchoscopy, fine needle aspiration (FNA), obtaining a sample of the fluid surrounding the lungs, surgery, or even a sample of mucus [25]. After a patient is diagnosed, their cancer is staged.

To stage a tumor, physicians use physical examination, patient history, biopsy, surgery, and an armament of constantly evolving diagnostic technologies such as imaging or blood tests. Imaging tests are frequently used in the evaluation of lung cancer patients, and can include standard chest X-rays, CT scans, spiral CT, MRI, PET, bone scans, or bronchoscopy [25].

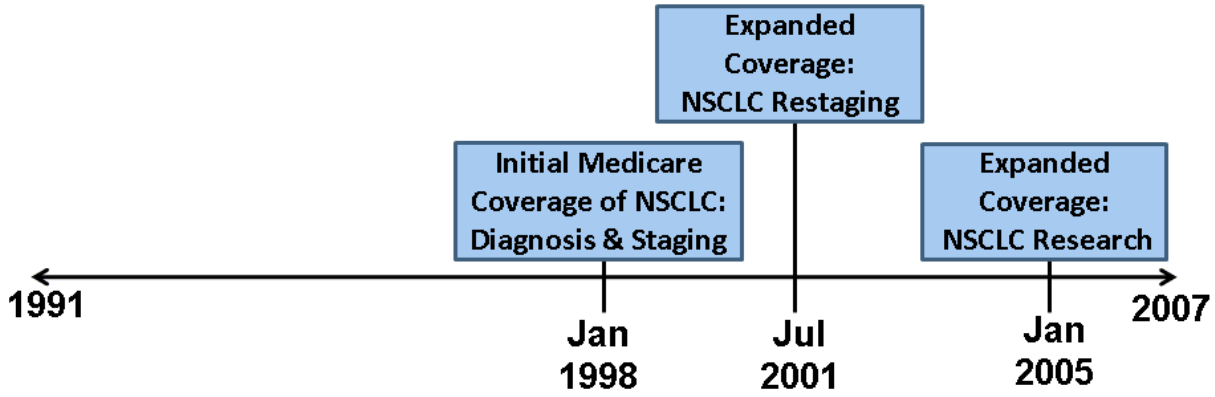
2.5 PET Evaluation of Lung Cancer

The most commonly used form of PET in oncology uses a radioactive mimetic of glucose called fluorodeoxyglucose (FDG), which is preferentially absorbed by cancer cells due to their high rate of metabolism. FDG-PET provides an improvement over traditional imaging modalities, such as CT scans, which only provide anatomical information such as the size or

presence of a lump or lymph node in the lungs. Studies demonstrating the ability of FDG-PET to differentiate benign, or harmless, nodules in the lung from metabolic active lung cancer were first published in 1992 [1]. In subsequent studies and comparisons with traditional imaging modalities, PET has been shown to provide a more sensitive and specific assessment of pulmonary nodules (small lumps in the lung) and metastasis of NSCLC lung cancer [6, 25, 28]. PET can be used to assess neurologic [29] and cardiovascular [30] disease. However, in recent years its greatest use by far has been related to cancer.[25]

The first use of PET scans to differentiate malignant and benign solitary pulmonary nodules (SPN) occurred in 1992. On January 1, 1998, PET was approved by Medicare for the characterization of SPNs and the initial diagnosis and staging of NSCLC (**Figure 2.2**). This initial coverage was expanded to include restaging of NSCLC on July 1, 2001. As of January 28, 2005, the use of PET was approved for all cancers, including NSCLC, provided that its use was part of a Medicare-approved research study [2]. Following the initial approval of PET in 1998, a number of studies have documented a rapid increase in PET among the general Medicare as well as other populations [3, 4, 31]. It is important to note that although PET scans can be used for non-cancer indications [2] in neurology[29, 32] or cardiology,[30] these claims are categorized separately within Medicare and can be differentiated from their use for cancer (see Chapter 4:Methods).

Figure 2.2: Timeline of Medicare coverage determinations for use in NSCLC[2].

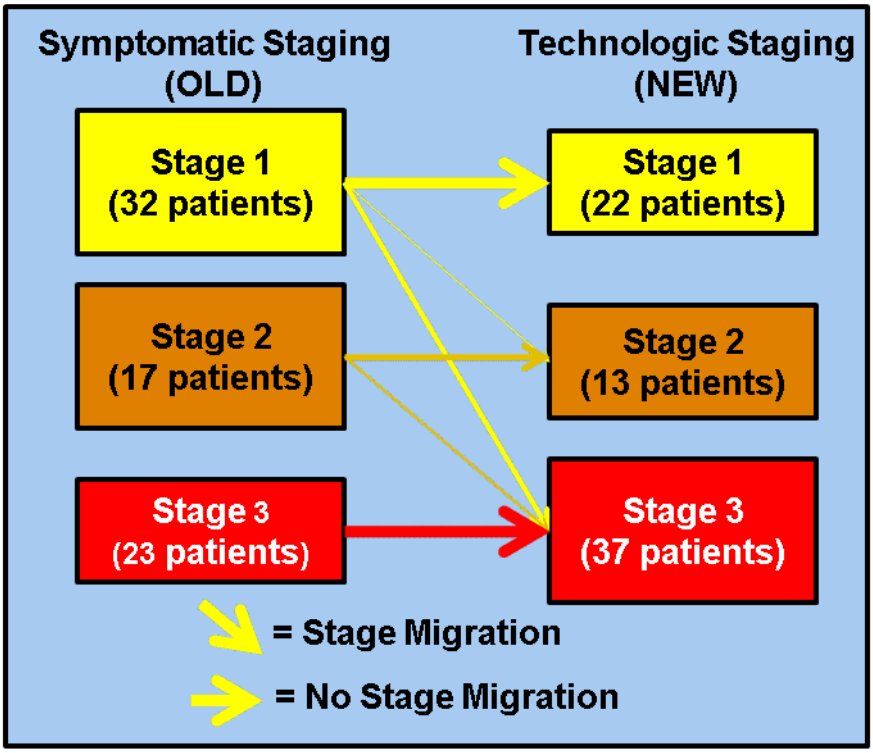


2.6 Stage Migration

In 1985, Feinstein and colleagues published a seminal paper that examined the staging of lung cancer patients before and after the introduction of several new diagnostic imaging technologies, including radionuclide scanning, CT, and ultrasonography [33]. In this study, the authors compared survival of two cohorts of patients, one treated between 1953 and 1964 and the other in 1977 and followed through 1982. After analyzing all available data, the later cohort appeared to have improved stage-specific survival compared to the earlier cohort. However, the authors noticed that the later cohort also exhibited differences in the stage distribution as compared to the earlier cohort. They hypothesized that observed differences in survival might be artifacts of the improved diagnostic techniques that had been introduced after 1964. They found that when they ignored the results of these tests and staged both cohorts using clinical manifestations such as anorexia, weight loss or fatigue (instead of technology-based assessments), both stage distribution and survival no longer differed between the two cohorts.

These results demonstrated that the use of novel, more sensitive diagnostic techniques had led to more aggressive staging of patients, but an artificial increase in patient survival (**Figure 2.3**).

Figure 2.3: Stage migration in NSCLC patients as a result of improved diagnostic technology (Printed with permission)



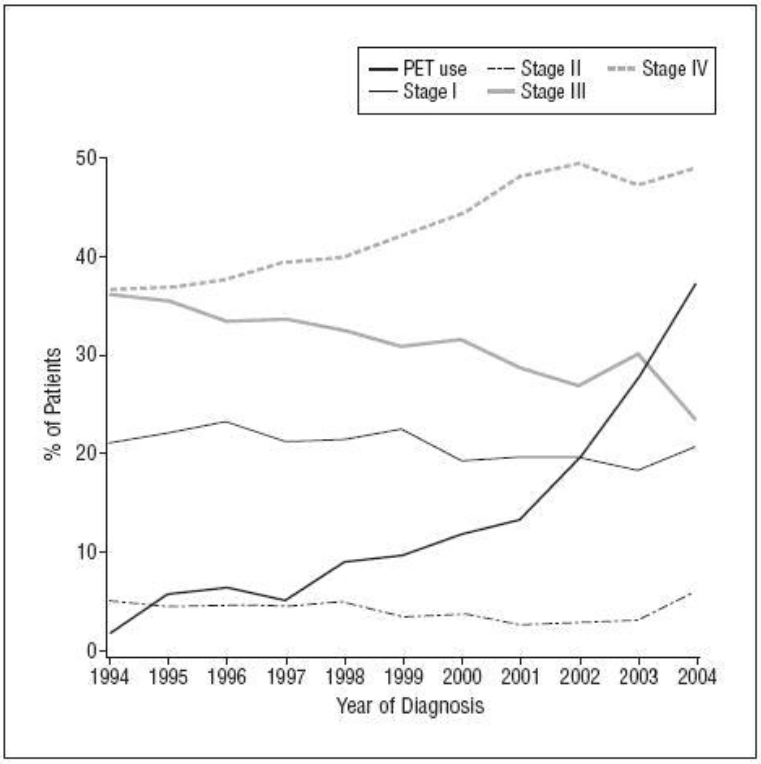
Adapted from Feinstein et al. 1985.

They named this phenomenon of stage migration in cancer the "Will Rogers Phenomenon" after American comedian and philosopher Will Rogers, who was reported to have made a remark regarding the American geographic migration during the great depression of the 1930s: "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

More than two decades later, Chee et al.[10] studied patients diagnosed with NSCLC between 1994 and 2004 within a California-based statewide cancer surveillance system. These patients were followed until study completion in 2006 or death. They found that in the years

following the introduction of PET (1999-2004) the number of stage IV cancers increased and the number of stage III cancers decreased (**Figure 2.4**) with an improvement in outcomes. However, stage migration must be carefully considered when evaluating the value of new, more sensitive diagnostic tests.

Figure 2.4: Stage migration in a large California private insurer lung cancer population (From Chee et al. [10] Printed with permission)



In addition to stage migration, earlier detection of cancer can result in artificial improvement in survival. Survival is measured from the time of diagnosis. Making an earlier diagnosis of the same cancer makes it appear that a patient has lived longer by shifting when the survival clock is started. This phenomenon, known as zero time-shift [33], also has the potential to

affect associations between patient survival and new diagnostic tests. In theory, a zero time-shift would be detected as an overall increase in the prevalence of disease; however, this has not been previously studied in NSCLC and PET, and is considered outside the scope of this proposal.

2.7 Changes in PET use

New or emerging technologies have not always disseminated uniformly among the American public, and PET has been no exception. Regional availability of PET varied significantly during its initial adoption. A study of regional imaging rates documented that in 1998, the rate of PET use was 15 times higher in New York than Dallas[34]. The same study suggested that heterogeneity in regional PET use has continued to persist as late as 2007, albeit at a reduced level.

Over the past two decades the use of non-invasive diagnostic imaging tests such as PET have shifted from radiologists to non-radiologists[35, 36]. In recent years, these tests have continued to shift from hospital outpatient facilities to private practices. This shift has been accompanied by the direct purchase or leasing of PET scanners by private practice physicians. The number of PET scanners owned or leased by non-radiologist, private practice physicians has increased seven-fold between 2002 and 2007 [37]. The vast majority of physicians (95%) now in possession of PET scanners are in internal medicine, medical oncology, cardiology, radiation oncology, or primary care. The changing use of PET over time has been observed in other countries in recent years [38].

In order to address the changing landscape of PET use in the oncology community, in 2005 the Centers for Medicare & Medicaid Services (CMS) began providing coverage for any PET scan involved in oncology provided that it was part of "Coverage with Evidence

Development" (CED) [2]. In order to fully capitalize on potential evidence from CED, CMS allowed the creation of the National Oncologic PET Registry (NOPR) [39]. The NOPR is an internet-based, prospective registry sponsored by the Academy of Molecular Imaging (AMI) and managed by the American College of Radiology (ACR) through the American College of Radiology Imaging Network (ACRIN). The NPOR obtains information regarding physician treatment plans before and after performing PET. Initial findings from the NPOR have suggested that roughly one of three physicians will change their decision to treat or not treat following a PET scan[40]. The NPOR only receives information for PET scans provided as part of CED, and therefore does not include the use of PET for previously approved indications, including NSCLC. Findings from the NPOR study may not be generalizable to PET use in NSCLC or other approved PET indications. In response to findings from the NPOR, CMS announced a decision to expand coverage to include a single PET scan for any solid tumor or myeloma in April 2009[41]. Following this expansion of coverage, NPOR has continued to collect information on PET usage that remains covered under CED.

2.8 Disparities in Medical Technology Use

Disparities in race, gender, and age have been observed with regards to cancer health care access, treatment, and survival[22,42-59]. In general young, white, educated, high income, and urban individuals are more likely to receive emerging health care services. A study of elderly Medicare patients observed that whites were more likely to receive 23 different procedures and tests than blacks. In particular, they found that whites especially had an advantage with regards to receiving new or higher-technology services [42]. Studies of other cancer diagnostic or screening technologies have demonstrated differential use by demographic characteristics, with

older, black, rural, poorly-educated, females being least likely to receive the newest technology for colorectal cancer screening. PET scanners are expensive resources that may not be available at disadvantaged hospitals. African Americans and whites are often treated at different hospitals [47], with hospitals that treat large proportions of African American patients being less likely to perform emerging medical procedures on any of their patients [22].

A study of SEER-Medicare patient outcomes between 1991 and 2002 found a significant difference in survival between blacks and whites with NSCLC in overall mortality. Blacks with stage III-IV disease fared worse than whites with stage III-IV disease during the most recent study period, which ranged from 2000-2002 period, but not earlier periods [56]. Emerging medical technology such as PET could be culprits in reintroducing disparities in NSCLC management and outcomes.

2.9 Significance and contribution

Concerns have emerged that the rapid adoption of emerging medical devices and imaging technologies may be unduly influenced by less stringent FDA approval requirements than those required for new drugs [60], high profit margins [61], and inadvertent payment incentives [20]. Not surprisingly, high-end imaging services such as CT, MRI, and PET are among the most frequent sources of competition acknowledged among hospitals and physicians [62]. There are additional concerns that the use of high-end imaging appears to be additive in nature and does not replace the need for conventional imaging methods and results in increased healthcare utilization and costs [63]. Previous analyses have suggested that the high cost of PET, reimbursed by Medicare in 2004 at $1,774 per scan [64], may be in part justified by a purported association with improved NSCLC patient survival [9,11]. However, high cost and ethical considerations have precluded the

ability to conduct large, adequately-powered randomized, controlled trials to definitively assess the overall indirect effect of PET on patient outcomes. Epidemiologic assessments of PET have not fully eliminated potential bias due to either selection bias or stage migration [9], or have not been conducted in the Medicare cancer population [10].

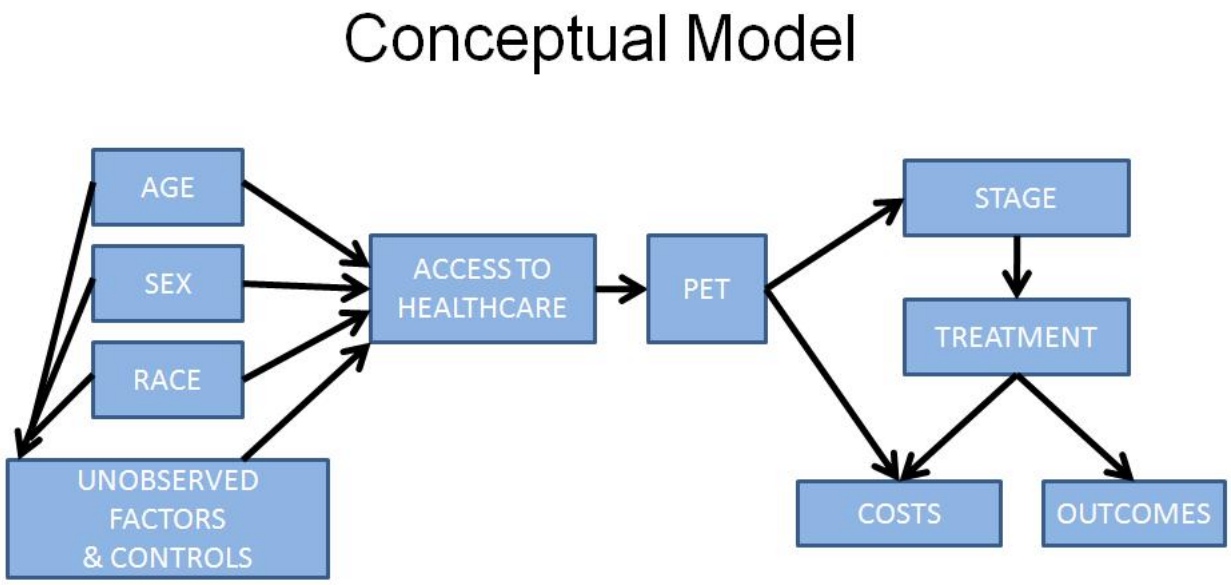
Fully understanding the utilization of PET and how it affects evaluation, staging, treatment, and health care utilization in NSCLC patients has considerable implications for the establishment of future imaging guidelines. The proposed study will examine the possibility of PET as a culprit for promoting disparities in NSCLC management and outcomes. By carefully characterizing and controlling for selection bias and stage migration, the proposed study will arrive at population level estimates of the association of PET with both favorable patient outcomes and unfavorable health care costs in order to best inform the balance of future health care policy.

CHAPTER 3: RESEARCH QUESTIONS AND HYPOTHESES

The goals of the proposed study are to: 1) characterize the spread of PET throughout the Medicare lung cancer population, 2) assess the presence and magnitude of PET-induced stage migration in the Medicare lung cancer patient population and its effect on patient outcomes, and 3) estimate the effect of PET on healthcare costs and utilization in the context of stage migration.

Aim1 will examine the dissemination of PET into the Medicare lung cancer patient population from 1998 to 2005. The conceptual model (**Figure 3.1**) examines the influence of age, gender, and race on the likelihood of a patient receiving PET. I hypothesize that this effect is mediated, in part, through general accessibility to health care. A previous study by Farjah et al. [65] found that younger, female, whites had higher rates of advanced diagnostic tests in the Medicare lung cancer population.

Figure 3.1: Conceptual model of the relationship between demographic factors, access to healthcare, PET use, staging, treatment, costs, and outcomes.



3.1 Specific Aim 1

Research Question 1: How has PET diffused in the Medicare NSCLC patient population with regards to age, race, and gender over time?

H1a: During the initial adoption of PET, patients who tend to have the most access to health care were most likely to receive PET. Specifically, younger, white, females will be most likely to receive PET.

H1b: Receipt of PET will be initially biased heavily towards younger, white, females. As PET adoption becomes more widespread, the association between PET use and age, gender, and race will decrease.

Specific Aims 2 and 3 will examine the magnitude of PET induced stage migration and its effects on outcomes, healthcare utilization, and costs. The conceptual model (**Figure 3.1**) is based on the hypothesis that PET use will affect patient staging, which will in turn affect patient

treatment and management, which will result in changes in patient outcomes, health utilization, and costs. The use of PET will affect health care costs through the direct cost of the imaging scan.

3.2 Specific Aim 2

Research Question 2a: Was the adoption of PET associated with stage migration in the overall Medicare NSCLC patient population over time?

H2a1: The proportion of beneficiaries diagnosed with stage IV NSCLC cancer in the overall Medicare population will be positively correlated with the proportion of beneficiaries receiving PET for those diagnosed with NSCLC between 1993 and 2005.

H2a2: Individuals diagnosed in the post-PET subgroup (2004-2005) will demonstrate a significant increase in the relative proportion of stage IV cancers compared to pre-PET and initial-PET subgroups (1993-1994 and 1998-1999).

Research Question 2b: Did the adoption of PET result in differential stage migration over time in subsets of the Medicare lung cancer patient population that experienced differing rates of PET use?

H2b1: Younger, white, females in the post-PET subgroup (2004-2005) will demonstrate a significant increase in the relative proportion of stage IV lung cancers as compared to the pre-PET subgroups (1993-1994 and 1998-1999), whereas old, minority, males will not.

H2b2: The older, minority, male population will have experienced slower rates of PET adoption and will see less stage migration between 1993 and 2005 than the younger, white, female population.

Research Question 2c: What is the magnitude of PET-associated stage migration?

H2c: A beneficiary receiving one or more PET scans will be more likely to be diagnosed with stage IV cancer than a beneficiary who has not received a PET scan.

Research Question 2d: Previous studies by Farjah et al. [9] and Chee et al.[10] have suggested strong associations between PET use and survival in which the use of PET is associated with 30-50% increased survival rates in NSCLC patients. It is possible that previously observed associations between PET use and survival are a result of selection bias or stage migration. Is there a positive association between PET use and improved patient outcomes after controlling for both selection biases and stage migration?

H2d: Beneficiaries receiving one or more PET scans will have increased 2-year survival compared to beneficiaries who did not receive PET. However, the observed association between PET use and increased survival will be smaller in magnitude or disappear altogether after correctly adjusting for PET selection biases estimated in Aim 1 and PET associated stage migration estimated in Aim 2.

3.3 Specific Aim 3

Research Question 3a: Is differential treatment of lung cancer associated with PET use in the overall Medicare lung cancer population?

H3a1: Beneficiaries receiving one or more PET scans will be more likely to have a diagnosis of stage IV cancer, which will reduce the number of overall patients receiving futile surgical treatment with a curative intent in the 2004-2005 cohort.

H3a2: Beneficiaries receiving one or more PET scans will on average receive more aggressive non-surgical treatment (radiation and chemotherapy) than those who did not receive PET in the 2004-2005 cohort.

Research Question 3b: Is the cost of treating lung cancer associated with the use of PET?

H3b1: PET use will be associated with higher total costs and lower surgical costs in the overall NSCLC Medicare population. Higher costs will be associated with PET use as a result of an association between PET and health care access. Total surgical costs will be reduced due to a reduction in the number of futile thoracotomies (unnecessary surgery).

H3b2: Populations with higher PET propensity will experience overall cost savings relative to lower PET propensity populations in the post-PET subgroup (2004-2005) compared to pre-PET subgroups (1993-1994 and 1998-1999) due to sparing of unnecessary surgical treatment costs of correctly diagnosed stage IV patients.

CHAPTER 4: METHODS

4.1 Overview

The overall objectives of the project are to characterize the following phenomena within the Medicare lung cancer population: 1) adoption of PET, 2) PET-induced stage migration and its effect on patient outcomes, and 3) changes in health care utilization as result of PET use. To address these objectives I conducted a secondary analysis of the SEER-Medicare linked dataset composed of SEER data for the years 1993 through 2005 and linked Medicare data for the years 1992 through 2007. Proposed research questions, hypotheses, and analyses are summarized by aim in **Table 4.1**.

4.2 Data

4.2.1 Medicare Claims data

Medicare is the nation's single largest medical insurer, providing coverage for 97% of the U.S. population ages 65 and older[66]. Medicare standard analytic files include denominator files and corresponding inpatient, outpatient, carrier, and durable medical equipment claims from the CMS. The inpatient files contain institutional claims for facility costs covered under Medicare Part A, and the outpatient files contain claims by institutional outpatient providers (eg, hospital outpatient departments, ambulatory surgery centers). The carrier files contain provider claims for services covered under Medicare Part B. The denominator files contain beneficiary identifiers, sex, race/ethnicity, birth dates, dates of death, ZIP codes, and information about program

eligibility and enrollment [67]. Enrollment information from the denominator files are included in the provided SEER Patient Entitlement and Diagnosis Summary File (PEDSF) file. The SEER linked Medicare data provides both cancer and non-cancer controls matched by geographic region [66]. Medicare claims describe Medicare payments, and have been used routinely in the literature to determine the cost of services to Medicare and estimate overall health care expenditures.[68]

Table 4.1: Proposed Research Questions, Hypotheses, and Analyses Summarized by Aim

Hypotheses		Analysis	Cohort
AIM 1 – Q1: How has PET disseminated within Medicare?			
H1a	White, young, females will be more likely to have received PET	Pr(PET) = f($\beta_0 + \beta_1$ Race + β_2 Sex + β_3 Age + β_4 Year)	Dataset 1 (1998-2005)
H1b	As availability of PET increases with year of diagnosis, the association between PET and race, sex, and age will decrease	Pr(PET) = f($\beta_0 + \beta_1$ Race + β_2 Sex + β_3 Age + β_4 Year + interaction w/ race, sex, and age)	
AIM 2 – Q2A: Was PET adoption associated with stage migration in the overall Medicare population?			
H2a1	Prevalence of stage IV cancer will be correlated with PET use in the overall Medicare population between 1993-2005	Descriptive plot	Dataset 2 (1993-2005)
H2a2	Prevalence of stage IV cancer will be highest in the post-PET era	Chi-Squared test	Dataset 3 (Post vs Pre-PET)
AIM 2 – Q2B: Did subsets of the Medicare population with differential PET adoption exhibit differential stage migration?			
H2b1	As a group, young white females will experience exaggerated stage migration compared to old black males between 1993-2005	Descriptive plot	Dataset 2 (1993-2005)
H2b2	As a group, young white females will have more stage IV cancer in the post-PET era, while old black males will not	Chi-Squared test	Dataset 3 (Post vs Pre-PET)
AIM 2 – Q2C: What is the magnitude of PET-associated stage migration?			
H2c	Receipt of PET will be associated with increased stage IV cancer	Pr(*Stage IV*) = f($\beta_0 + \beta_1$ PET)	Dataset 3 (Post-PET only)
AIM 2 – Q2D: Is PET use associated with increased two-year survival?			
H2d	Beneficiaries receiving PET will have unchanged two-year survival after adjusting for selection bias and stage migration	Pr(*2yr-Survival*) = f($\beta_0 + \beta_1$ PET + β_2 Stage + βPET*Stage)	Dataset 3 (Post-PET only)
AIM 3 – Q3A: Is PET use associated with altered patient management?			
H3a1	Surgical treatment will decrease over time w/ the introduction of PET. PET use will be associated with less frequent surgical treatment	Pr(*Chem, Radiotherapy, or Surgery*) = f($\beta_0 + \beta_1$ PET + β_2 Stage + β *Year*)	Dataset 2 (1996-2005)
H3a2	PET use will be associated with more frequent non-surgical therapy		
AIM 3 – Q3B: Is PET use associated with increased total health care utilization?			
H3b1	PET use will be associated with higher non-inpatient costs in the overall Medicare population due to increased health care access	*Non-Inpatient Costs* = $\beta_0 + \beta_1$ PET + β_2 Stage + β*Year* +/- β*Treat*	Dataset 2 (1996-2005)
H3b2	Inpatient/Surgical costs will decrease over time as a result of reducing futile thoracotomy costs following the adoption of PET	*Total and Inpatient Costs* = $\beta_0 + \beta_1$ PET + β_2 Stage + β*Year* +/- β*Treat*	

See sections 4.3.1 and 4.4.1 for detailed description of datasets 1-3.

4.2.2 SEER (Surveillance, Epidemiology, and End Results) data

The SEER cancer registry is a large population-based cancer registry that tracks the incidence of all cancers in selected geographic regions within the United States. The registry first began tracking cancers in 1973, and in 1991 first began linking with Medicare claims [66]. SEER-Medicare data have since provided a unique opportunity to allow population-based analysis of cancer care [69]. Patients within the SEER registry are considered to provide a reasonable representation of the overall U.S. population, however it should be noted that compared to the overall U.S. population, patients within the SEER registry are overall more likely to be non-white, live in non-poverty areas, and live in urban areas[66]. Information collected through SEER is provided within the SEER Patient Entitlement and Diagnosis Summary File (PEDSF) and includes patient demographics, date of diagnosis, cancer stage, histology, grade, treatment provided within 4 months diagnosis, and cause of death. The registry does not include information about cancer screening, how a cancer was diagnosed, treatment beyond 4 months after diagnosis, or long-term disease status [66].

The combined SEER-Medicare data have been used previously to study a number of aspects or features that affect cancer care quality and include sociodemographics [67], physician[70] and hospital[71] characteristics, surgery[72], chemotherapy[73], radiation[74], comorbidities[75], complications[76], screening[77], relapse[78], and costs[68]. For the purposes of this study, the key information gained from the SEER portion of the SEER-Medicare linked data will be the diagnosis of NSCLC, AJCC cancer stage, and patient and local demographics. The key information gained from the Medicare linked claims data will be PET use, cancer treatment, and health care costs. A list of all variables and corresponding data sources is shown in **Table 4.2**.

Several registries were added to SEER in 2000. Comparisons within the SEER-Medicare data that include years before and after 2000 will be limited to SEER registries present in all years.

Table 4.2: Summary of All Variables and Data Sources

Variable	Variable Type	Source	Derivation/Notes
Age	Continuous	SEER - PEDSF	Age at diagnosis
Cumulative incidence (observation time)	Continuous	SEER - PEDSF	Time from diagnosis to death, hospice, HMO, or two years, whichever is shortest
Diagnosis date	Continuous	SEER - PEDSF	Monthly
Education	Categorical	SEER – PEDSF	Zip code level quartiles
Gender	Dichotomous	SEER – PEDSF	
Income	Categorical	SEER – PEDSF	Zip code level quartiles
Marital Status	Categorical	SEER – PEDSF	
Race	Categorical	SEER – PEDSF	
Region	Categorical	SEER – PEDSF	
Residence Type	Categorical	SEER – PEDSF	
Stage	Categorical	SEER – PEDSF	-AJCC 3rd edition through 2003, AJCC 6th edition afterwards -Modified AJCC 3rd edition through 2003 -SEER summary staging -SEER historic staging
2-yr Survival	Dichotomous	SEER – PEDSF	Alive or deceased at 2 years
Chemo/ Radiation	Dichotomous	SEER – PEDSF Medicare	Indicates if the patient had any record of chemotherapy or radiotherapy in either SEER or Medicare claims. Medicare HCPS codes are used per Farjah et al. (2009).
Surgery	Dichotomous	SEER – PEDSF Medicare	Indicates if the patient had any record of chemotherapy or radiotherapy in either SEER or Medicare claims. Medicare HCPS codes are used per Farjah et al. (2009).
NCI Comorbidity Index	Continuous	Medicare	Determined using Medicare claims in the year prior to cancer diagnosis
Total Health Care Costs	Continuous	Medicare	Line item summed Medicare payments using all patient claims from all inpatient, outpatient, carrier file, medical device file, and home health file. Technically these are payments, not costs. They do not include patient co-pays or deductibles, but instead indicate the amount that Medicare paid for a given service.
Inpatient Health Care Costs	Continuous	Medicare	Total Health Care Costs, limited to inpatient file.
Non-Inpatient Health Care Costs	Continuous	Medicare	Total Health Care Costs, excluding inpatient file.
PET receipt	Dichotomous	Medicare: Carrier Files Outpatient Files	Determined by the presence of any one of the following HCPCS during the specified window: 78810-78816, G0125, G0126, G0163, G0164, G0165, G0210-G0228, G0231-G0234, G0213-G0215, G0226-G0228, G0235, G0252, G0253, G0254, G0296, G0330, G0331
Distance to PET	Continuous	Derived	Zip code based distance calculation between patient and nearest zip code with a PET facility
PET facility / provider	Dichotomous	Derived	Derived by identifying the first date at which any PET providing or referring physician files a claim at that facility. From that date forward, the facility is considered a PET facility.
PET propensity score	Continuous	Derived	Logistic Regression

NCI: National Cancer Institute
HCPCS: Healthcare Common Procedure Coding System

4.3 Specific Aim 1

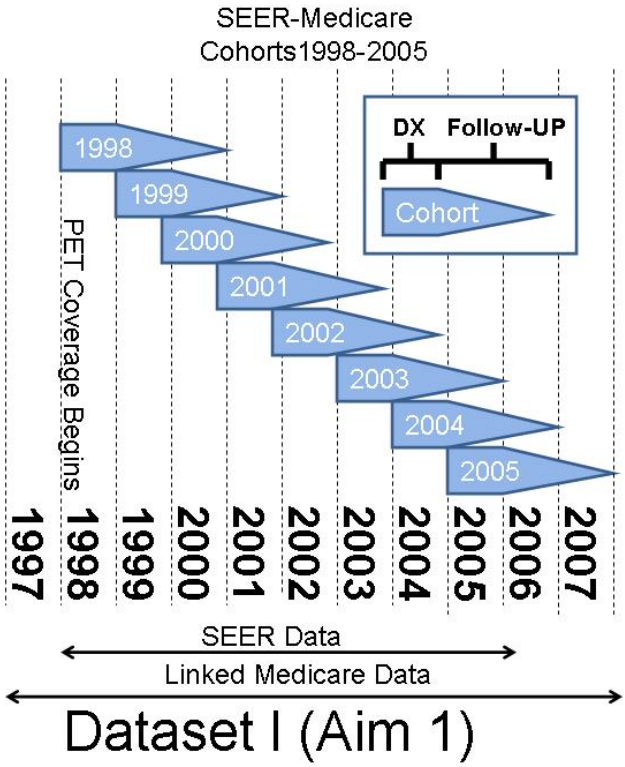
Characterize the dissemination pattern of PET from 1998 to 2005 in the SEER-Medicare NSCLC patient population. Previous analyses have demonstrated a significant selection bias in the application of PET, finding that PET use in the Medicare lung cancer patient population is significantly higher in educated, high income, white, married individuals with early stage tumors[9,10]. It is not clear how the severity and magnitude of these selection biases have changed over time. Non-uniform dissemination of PET and/or patient selection biases may have confounded previous studies of the value of PET technology. This aim examines dissemination patterns of PET in a nationally representative sample of lung cancer patients. Specifically, I hypothesize that the increased use of PET in Medicare beneficiaries with NSCLC will be observed among patients who are young, white, and female. I hypothesize that non-uniform dissemination and selection biases were most severe following the introduction of PET and that these biases have lessened with wider adoption of PET.

4.3.1 Cohort Structure and Inclusion/Exclusion Criteria

The study cohort for Aim 1 is composed of the SEER-Medicare sample for the years 1998 through 2007 (**Figure 4.1**). Because Aim 1 relies on the comparison of beneficiaries who do and do not receive, PET, the study population is restricted to years in which some beneficiaries received PET. Fewer than 5% of Medicare beneficiaries diagnosed with NSCLC before 1998 received any PET scans. [79] The proportion of beneficiaries receiving PET continued to be low for patients diagnosed in 1998 in preliminary analyses (not shown), with only 1.3% of all lung cancer beneficiaries having undergone one or more PET scans within two years of their diagnosis. The proposed SEER-Medicare cohort will be restricted to 1998 and later to ensure

that each cohort year contains an adequate proportion of PET receiving beneficiaries. The exclusion of the 1996 and 1997 cohorts may help to avoid potential bias caused by differences in the timing of PET administration between the 1996 and 1997 cohorts and later cohorts. Since PET was not approved until 1998, individuals receiving PET within the 1996 and 1997 cohorts would have likely have done so after one to two years of their cancer diagnosis. As a result, PET use within the 1996 and 1997 cohorts would be mostly used for restaging or treatment evaluation and might systematically differ from PET used in later cohorts for diagnosis or staging.

Figure 4.1: Aim 1 Cohort Structure. Dataset/Population 1.



The basic cohort structure identifies individuals with a SEER-based diagnosis of NSCLC lung cancer similar to a previous study by Farjah et al. (2009)[9]. Patients were excluded if they were diagnosed at autopsy/death, were younger than 66 years old, did not have NSCLC pathology, had another malignancy in the year prior (using Medicare claims), and did not have both part A and B coverage, or were enrolled in a health maintenance organization (HMO).

Patients were additionally required to have at least one Medicare based *ICD-9-CM* diagnosis of lung cancer (162.2, 162.3, 162.4, 162.5, 162.8, 162.9, or 231.2) on a carrier, inpatient, or outpatient claim within the two months prior to or following the SEER NSCLC cancer diagnosis. Each patient was followed for two years from the date of diagnosis (**Figure 4.1**). This distinct time frame provides a well-delineated period over which cancer-related imaging procedures can be assessed [3]. Additionally, confining the analysis to a two-year period allows for equivalent follow-up for all patient cohorts through the 2005 cohort.

To be considered a new-onset or incident case, beneficiaries were required to have been eligible for fee-for-service Medicare for a minimum of one year (i.e., must be ages 66 or older) to provide a year of prior claims from which comorbidities can be determined. A summary of datasets and cohorts used in each aim are provided in **Table 4.3**.

Table 4.3: Summary of Datasets and Cohorts

Dataset	SEER data (Years of Diagnosis)	Medicare Claims	Aims	Motivation
1	1998-2005	1997-2007	1	Capture continuous trends during period of PET adoption
2	1993-2005	1992-2007	2, 3	Capture continuous trends during period before and during PET adoption
3	Pre-PET (1993-1994) Initial-PET (1998-1999) Post-PET(2004-2005)	1992-1996 1997-2001 2003-2007	2, 3	Characterize discrete cohorts that occured well before, just before, and at peak PET usage

4.3.2 Study Variables and Controls

The key dependent variable studied in Aim 1 was a dichotomous variable (receiving PET scans within two months prior to or following SEER lung cancer diagnosis). This variable will be operationalized using HCPCS codes within the Medicare-linked carrier files. HCPCS codes

are used for various procedures or services for which Medicare claims must be billed. For the vast majority of medical services, HCPCS codes use current procedural terminology (CPT) codes developed and maintained by the American Medical Association (level I HCPCS codes). However, in cases where CPT codes do not exist or do not adequately describe a medical service for the purpose of Medicare, unique HCPCS codes are created (level II HCPCS codes). CPT/HCPCS codes corresponding to PET administration for Medicare beneficiaries differentiate between PET scans used to assess oncologic, cardiovascular, or neurologic conditions. I have used CPT/HCPCS previously to quantify PET scan use in the Medicare cancer patient population[3] (**Table 4.4**). PET can also be used for non-cancer related purposes. Medicare first covered the use of FDG-PET for non-cancer related purposes on July 1, 2001, for the assessment of heart tissue viability and seizures that are resistant to initial therapy. The goal of the current study is to assess the spread of PET use in the context of lung cancer care. As a result, only lung cancer related uses of PET or combined PET/CT (**Table 4.4**) will be counted as PET scans. Patients who have had one or more PET scan administered in the two months prior to the SEER month of diagnosis through 4 months later were considered to have received PET.

Table 4.4: PET CPT/HCPCS codes relevant to lung cancer

PET Type	CPT (Level I) codes	HCPCS (Level II) codes
PET- Tumor	78810-78813	
PET/CT -Tumor	78814-78816	
PET – NSCLC		G0125, G0126, G0210-G0212, G0234
PET – NOS*		G0235

*Site not otherwise specified

The key independent variables studied in Specific Aim 1 are year, PET availability (for propensity scoring) and patient demographics, specifically race, gender, and age. Race, gender, and age are all available from the SEER-PEDSF file. Race was defined as used in a previous study of PET and lung cancer by Farjah et al. [9] to allow comparability between studies and age will be modeled as a continuous variable (**Table 4.2**).

Table 4.5: Primary dependent and independent demographic variables.

Dependent Variable	Possible Values	Variable Type
Receipt of PET	One or more PET scans, No PET scans	Dichotomous
Primary Independent Variables		
Race	Black, Non-black	Categorical
Gender	male, female	Dichotomous
Elderly	>80 years old	Dichotomous
Year	Calendar Year	Continuous

Several factors may affect the decision to administer PET directly or represent general indicators of health care access (see conceptual model – **Figure 3.1**) and must be controlled (**Table 4.6**).

Table 4.6: Proposed Aim 1 control variables.

Control Variables	Possible Values	Variable Type
Distance to PET	<40 Miles, ≥ 40 miles	Dichotomous
Income (Census)	lowest quartile, upper three quartiles, missing	Categorical
Education (Census)	lowest quartile, upper three quartiles, missing	Categorical
Marital Status	married, not married, missing	Categorical
NCI Comorbidity Index	0, 1, 2+ comorbidities	Categorical
Region	SEER region	Categorical
Residence Type	metropolitan, urban, rural	Categorical

NCI: National Cancer Institute.

In a previous study by Farjah et al. [9], variables that were significantly associated with differential use of staging modalities in single variable analyses included region, income, education, marital status, and residence type (**Table 4.6**), all of which were included as controls. The comorbidity index developed by Klabunde et al. (2000) [80] was used to assess the severity of patient comborbidities using Medicare claims for the year prior to diagnosis. This comorbidity index was included as a control to adjust for the presence of other illnesses, which may affect patient treatment decisions.

I also controlled for distance of individuals to facilities offering PET. Distance of individuals to the closest PET facility was derived using Medicare carrier claims data. Each Medicare claim contains a unique identifier for both the performing and referring physician, as

well as a zip code for where a service was performed. Using carrier files, I determined the first date that a physician performed or referred a NSCLC patient for an oncologic PET. From this date forward, this physician and the location of service (zip code) were considered to be PET providers and PET providing locations, respectively. In the case that multiple claims are filed for the same PET scan (i.e. technical and professional components), the location closer to the patient was considered the location of service. Distance from patient to nearest PET location (using zip codes) was calculated. This distance to closest PET facility was determined at the end of the window used to assess PET use (4 months after diagnosis).

All control variables are summarized by aim in **Table 4.7**. All main dependent and independent variables are summarized by aim in **Table 4.8**.

Table 4.7: Summary of Control Variables by Aim

Control Variable	Possible Values	Variable Type	Aims
Elderly	Age > 80, Age ≤ 80	Dichotomous	All
Cumulative incidence (observation time)	Months	Continuous	3
Distance to PET	< 40 miles, ≥ 40 miles	Categorical	1
Education	lowest quartile, upper three quartiles, missing	Categorical	All
Gender	male, female	Dichotomous	All
Income	lowest quartile, upper three quartiles, missing	Categorical	All
Marital Status	married, not married, missing	Categorical	All
NCI Comorbidity Index	number of comorbidities	Continuous	All
Race	white, black, other, missing	Categorical	All
Region	SEER region	Categorical	All
Residence Type	metropolitan, urban, rural	Categorical	All
Stage	I, II, IIIA, IIIB, IV, Unknown	Categorical	2d
Advanced Disease	Early (I-IIIA), Advanced (IIIB-IV), Unknown	Categorical	2d, 3
Year of Diagnosis	1993-2005	Continuous	1a

NCI: National Cancer Institute

Table 4.8: Summary of Main Dependent and Independent Variables by Aim

Aim	Dependent Variables	Independent Variables
1	Receipt of PET (dichotomous)	Race Gender Age (categorical) Year (continuous)
2	Stage IV (dichotomous) Two-year Survival (percentile)	PET propensity (dichotomous) Receipt of PET
3	Surgery, Radiation, Chemo (dichotomous)	Receipt of PET (dichotomous) Year (categorical)
	Inpatient, Non-Inpatient, and Total Health Care Costs (continuous)	

4.3.3 Statistical Analyses

Aim1 tested hypotheses H1a and H1b, which suggest that younger, white, females will be most likely to receive PET during the initial adoption of PET and that this bias will decrease as PET becomes more widespread. I tested the initial hypothesis H1a using the following logistic regression model:

$$\Pr(PET) = f(\beta_0 + \beta_1 \text{Race} + \beta_2 \text{Sex} + \beta_3 \text{Age} + \beta_4 \text{Year} + \beta \text{Controls})$$

Eq 1A

A logit model was used in order to yield odds ratios indicating the relative likelihood that an individual received PET. In order to test the hypothesis H1b that demographic biases decrease with the adoption of PET, I added calendar *year* as an index of PET availability and interacted it with race, sex, and age. This second model was implemented as a linear probability model (LPM) in order to yield readily interpretable interaction coefficients.

$$\Pr(PET) = f(\beta_0 + \beta_1 \text{Race} + \beta_2 \text{Sex} + \beta_3 \text{Age} + \beta_4 \text{Year} + \beta_5 \text{Race} * \text{Year} + \beta_6 \text{Sex}* \text{Year} + \beta_7 \text{Age}* \text{Year} + \beta \text{Controls})$$

Eq 1B

4.3.4 Expected Outcomes, Strengths, Limitations, and Alternative Methods

Aim 1 assessed demographic biases in the administration of PET in the SEER-Medicare NSCLC patient population. Additionally, the aim assessed whether or not these biases are improving over time by observing whether discrepancies in PET use decrease from 1998 and 2005 as year increases.

The key variable assessed by Aim 1 is receipt of any PET. I performed sensitivity analyses to confirm that dissemination of PET is not sensitive to the six month window (2 months prior, 4 months following diagnosis) used to assess receipt of PET: I repeated the analysis using PET received within one year of diagnosis. I hypothesized that analysis results between the original and sensitivity analyses would yield qualitatively similar results over a range of PET receipt window lengths. Additional sensitivity analyses included controlling for SEER registry.

The key limitation of this aim is that only PET scans paid for by Medicare are recorded. Patients who pay for PET scans out of pocket or have additional, private insurance might be receiving PET scans prior to approval by Medicare. Given its cost, this phenomenon should occur infrequently. It may be possible to assess how often patients receive non-Medicare covered PET scans by comparing Medicare-based PET counts with SEER records for PET scans used in the two month period before and four months after diagnosis. An additional limitation was that because PET availability and time are highly correlated, it is not possible to disentangle

whether time or PET availability is responsible for changes in PET administration biases and so year alone will be examined for sake of conceptual clarity.

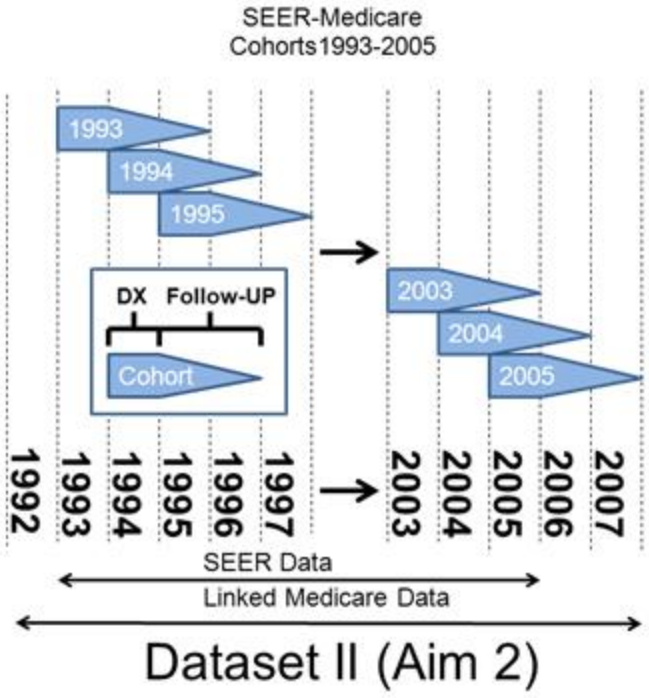
4.4 Specific Aim 2

Determine the presence and magnitude of PET-induced stage migration and the indirect association of PET use on patient outcomes. The introduction of novel screening or diagnostic methodologies can result in stage migration. An association between PET use and lung cancer stage migration has been suggested by a study of one large private insurer[10] and a small randomized trial[6]. However, the presence and magnitude of stage migration associated with PET has not been examined previously in the Medicare lung cancer patient population. PET is a diagnostic tool and cannot directly affect patient outcomes, but it can indirectly affect patient outcomes by changing patient treatment decisions. The existence of PET induced stage-migration in the Medicare lung cancer population may bias analyses of PET and must be controlled for to accurately assess the indirect effect of PET on patient outcomes. This aim determined the magnitude of PET associated stage migration within the Medicare lung cancer population and used it to derive updated estimates of the survival benefit associated with PET.

4.4.1 Study Population and Inclusion/Exclusion Criteria

Two distinct study cohorts were used in Aim 2. The first consisted of all individuals in the SEER-Medicare data diagnosed with NSCLC between 1993-2005 (**Figure 4.1**) and the latter referred to three specific subgroups within the SEER-Medicare data for patients diagnosed with NSCLC in 1993-1994 (pre-PET), 1998-1999 (initial-PET), and 2004-2005 (post-PET; **Figure 4.2**).

Figure 4.2: Aim 2 (part 1) cohort structure. Dataset/Population 2



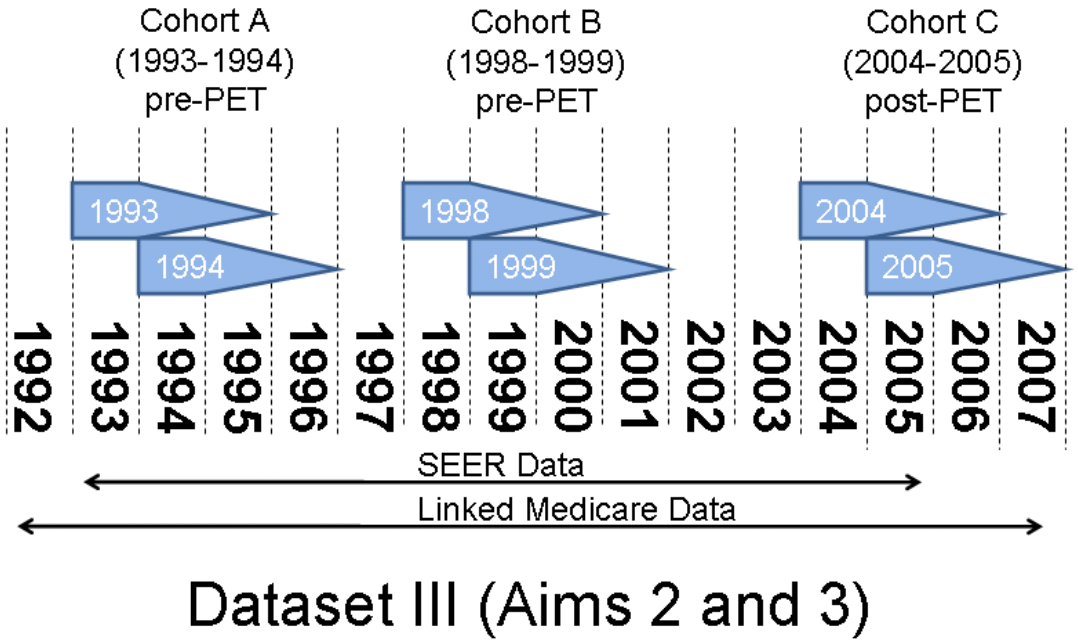
The study cohort for the first part of Aim 2 is composed of SEER data for the years 1993 through 2005 and linked Medicare data for the years 1992 through 2007. It was used to examine changes in stage distribution over time as a function of PET. The cohort includes a long time span in order to provide clear pre-PET and post-PET samples for investigating changes in stage distribution. The study population was selected to begin in 1993 in order to allow for a full year of Medicare claims in the year prior to establish NCI comorbidity index. Data from 1991 were excluded, as preliminary analyses of the Medicare 5% dataset suggest that the 1991 data may contain a different number of lung cancer cases and may systematically differ from other years.

The study cohort for the second part of Aim 2 (Dataset/Population III) was composed of SEER data subgroups diagnosed in years 1993-1994 (pre-PET), 1998-1999 (initial-PET), and 2004-2005 (post-PET), with linked Medicare data for the years 1992-1996, 1997-2001, and 2003-2007 (**Figure 4.3**). It was used to examine 2-year survival as a function of PET. Discrete subgroups were used to allow discrete statistical modeling of two periods before the widespread use of PET (pre-PET and initial-PET) and one period after (post-PET). Each subgroup combines two neighboring years of diagnosed patients in order to effectively double the sample size of the study. The earliest subgroup was composed of all patients diagnosed in 1993 or 1994 and followed for two years (pre-PET subgroup). The first use of PET in the diagnosis or staging of lung cancer was not published until 1992[81], suggesting that this pre-PET subgroup had zero or near zero PET exposure. The initial-PET subgroup was composed of all patients diagnosed in 1998 or 1999 and followed for two years. This subgroup was selected to begin in 1998, because consistent staging definitions for NSCLC were used between 1998 and 2003. The post-PET subgroup is composed of all patients diagnosed in 2004 or 2005 and followed for two years. The post-PET subgroup was chosen as the latest possible two-year subgroup with data. The use of PET has increased rapidly within Medicare lung cancer patients in recent years[3], and choosing the latest possible subgroup years ensured the largest portion of patients with PET.

Patient inclusion/exclusion criteria are those used in Aim 1. Two years of follow-up provides adequate follow-up to examine changes in NSCLC outcomes, especially for advanced stage disease (III and IV). The median survival of advanced stage IIIB or IV NSCLC has been generally placed at one year or less [82]. Two-year survival rates by cancer stage (see background) range from approximately 5% for stage IV cancer to 10-25% for Stage III, 40-50% for Stage II,

and 50-80% for Stage I [27, 82]. The two-year window for follow-up is therefore expected to capture most failures for advanced stage III and IV patients, which are the focus of this study.

Figure 4.3: Aim 2 (part two) and Aim 3 cohort structure. Dataset/Population 3.



4.4.2 Study Variables

The key dependent variables in Aim 2 are: 1) lung cancer stage distribution and 2) 2-year survival (**Table 4.9**). Lung cancer stage distribution was measured as the proportion of patients having stage IV lung cancer, as PET-induced stage migration has been previously shown to primarily result in a shift from stage III to stage IV cancer [10]. AJCC cancer stage is provided in the SEER registry data. It should be noted that SEER staging uses all available clinical, surgical, and pathological data in order to determine cancer stage, some of which may not have been available to physicians prior to making treatment decisions. Alternative stage definitions within

SEER include SEER modified AJCC 3rd edition, SEER summary stage, and SEER historic stage. Overall survival in lung cancer patients is typically defined using median survival or five-year survival. However, the cohorts defined within this study span two years. To allow all cohorts to have equal follow-up time, survival was assessed at two years. Two-year survival was obtained using the SEER-reported death date, which is confirmed by multiple sources including those used by Medicare [67]. Two-year survival was chosen over median survival, as the original work on stage migration by Feinstein et al. (1985) [33] found that percent survival was more amenable to analyses of stage migration. Unlike median survival, the percent survival of a group changes predictably as members are added or removed, facilitating analyses of stage migration and shifting between groups.

The key independent variable was having undergone any PET scans between two months prior to and 4 months following diagnosis. PET was only examined within these six months of diagnosis to help limit observed PET scans to those used for diagnostic or staging roles and to coincide with SEER-provided stage, which is based on information obtained within four months following diagnosis.

Table 4.9: Aim 2 dependent and independent variables

Dependent Variables	**Possible Values**	**Variable Type**
Lung Cancer Stage IV	Stage IV, Non-stage IV (I,II,III)	Dichotomous
Overall Two-Year Survival	Survived, Died	Dichotomous
Independent Variables		
PET propensity score*	0-100%	Continuous
PET within two years of diagnosis	Any PET, No PET	Dichotomous

*PET propensity score was used for propensity score matching sensitivity analysis. PET propensity score was not used as an independent variable in a regression model, but was instead generated as part of the matched analysis.

Control variables that might have affected patient stage or outcomes were used including both the demographic and control variables (**Table 4.7**) used in Aim 1 (age, race, sex, income, region, and education). Patient comorbidities were included as controls using the NCI

combordity index[80], which has been shown previously to affect overall survival in cancer patients[75,80,83].

Previous studies of PET administration have demonstrated that white, educated, high-income, married females are most likely to receive PET[9,10]. It is likely that receipt of PET is associated with better access to health care. Analyses that use receipt of PET as an independent variable will capture the effect of access to health care, and will detect an artificial association between PET receipt and patient survival that is actually due to health care access. To mitigate this potential source of omitted variable bias (health care access), patients were additionally matched by their likelihood, or propensity, of receiving PET, explored tangentially in Aim 1. The probability that each patient received PET was calculated using a probit model and the variables described in equation 1A along with year interaction terms. The purpose of this PET propensity score was to model PET selection bias. The PET propensity score was be calculated using data from 1996-2005. The PET propensity score is a continuous variable that can, in theory, range from 0 to 100. The identification of equally likely PET candidates was used to provide matched controls in sensitivity analyses.

4.4.3 Statistical Analyses

Using Medicare-SEER data, the stage distribution of Medicare NSCLC patients was examined from 1993-2005 (dataset/population II). The overall distribution of stage I, II, III, and IV lung cancer was plotted over time alongside the frequency of PET use. Stage distribution in the overall Medicare NSCLC is expected to lie somewhere between populations with high and low PET propensity to illustrate stage migration associated with the introduction of PET in the overall Medicare population. This was repeated in the likely and unlikely PET candidate

populations, with the hypothesis that stage migration would be larger in sub-populations that were more likely to receive PET.

The second set of statistical analyses used study population 3 to perform more specific subgroup comparisons. The overall stage-specific incidence of lung cancer patients was compared in aggregate between subgroups diagnosed in 1993-1994, 1998-1999, and 2004-2005 corresponding to two pre-PET and one post-PET utilization time points (study population 3). The frequency of stage III and stage IV lung cancer was compared using chi-square tests, with the hypothesis that stage IV lung cancer rates increased at the expense of stage III cancers following the introduction of PET.

Within the 1996-2005 subgroup, logistic regression was used to assess the magnitude of PET-induced stage migration from stage III to stage IV disease. The following logit model was used to examine to what extent the administration of PET resulted in stage III cancers being reclassified as stage IV cancers:

$$\Pr(\textit{Stage IV}) = f(\beta_0 + \beta_1 \text{PET} + \beta \text{ Controls} + \varepsilon)$$

Eq 2A

I tested the hypothesis that receipt of one or more PET scans was associated with improved 2-year survival, correcting for both PET-induced stage migration and selection bias (hypothesis H2d). To correct for PET selection bias, an additional sensitivity analysis was performed among equally likely PET candidates (propensity score matched). As an additional precaution, patients who did not survive for at least two months were excluded from the analysis, since such patients might have poor performance status and appear sick enough at diagnosis to discourage unnecessary PET. The inclusion of extremely sick patients might have otherwise

resulted in a spurious association between PET and improved survival. PET is suspected to cause migration from stage III to stage IV classification. Two-year patient survival was compared using the following model within stage I, stage II, and late stage (stage III or IV) disease.

$$\textit{Two-Year Survival} = f(\beta_0 + \beta_1 \text{PET} + \beta \text{ Controls})$$

Eq 2B

Lastly, two-year survival was plotted in unlikely vs. likely PET candidate populations over the 1993-2005 period both in aggregate and broken down by stage. The hypothesis was that two-year survival increased in populations receiving PET relative to those that did not. All regression analyses in Aim 2 was carried out using clustered errors (at the level of SEER registry) [81].

4.4.4 Expected Outcomes, Strengths, Limitations, and Alternative Methods

Successful completion of this aim attempted to identify the presence and magnitude of stage-migration associated with increased PET scan use among the Medicare population. In addition, it would provide more accurate estimates of PET benefit in lung cancer patient outcomes.

The previous study of PET-induced stage migration by Chee et al. 2008, [10] did not find an association between PET and stage I and II cancer incidence. PET should not be able to provide a real survival advantage in these groups since PET would not result in a change of clinical management. However, increased survival of stage I or II patients could be observed for two reasons. First, patients receiving PET may receive more thorough health care and treatment. For

example, they may have better access to care and PET scans if they live in an urban vs. rural environment, are uneducated, or are poor, etc. I will try to adjust for this by limiting the analysis to likely PET candidates. Second, PET could result in a zero time shift, whereby lung cancers are diagnosed sooner than they normally would have. A zero time shift would artificially result in improved survival. An independent means of confirming the presence of a zero time shift would be to examine the overall prevalence of lung cancer in the general Medicare population as a function of Year. If lung cancer prevalence increases overall with PET, it would suggest the presence of a zero time shift.

4.5 Specific Aim 3

Assess the effect of increased PET usage on lung cancer patient health care utilization and costs within the Medicare population. PET scan usage and costs are among the fastest growing areas of health care utilization in the Medicare cancer patient population[3]. PET scan use in lung cancer patients outside the Medicare cancer patient population has resulted in changes in lung cancer staging and management[5, 7]. Stage migration within Medicare (evaluated in Aim 2) and resultant altered patient management could affect utilization of additional health care resources, and could potentially decrease health care costs in the Medicare lung cancer patient population if unnecessary treatment, particularly futile thoracotomy, is avoided as a result of increased PET imaging discovering occult metastatic disease.

4.5.1 Study Population and Inclusion/Exclusion Criteria

Aim 3 used the same inclusion/exclusion criteria and subgroup cohort structure described in Aim 2 (part two, **Figure 4.2**) to perform discrete analyses between 1) pre/initial-PET and post-PET periods and 2) within the post-PET period as well as continuous analysis of patients

diagnosed between 1996-2005 (subset of Aim 2 dataset, part one). For each patient health care expenditures and treatments were calculated based on Medicare claims made during the 1-year period following diagnosis.

4.5.2 Study Variables and Controls

The key dependent variables in Aim 3 were treatment and total health care payments. Treatment options for lung cancer include surgery, radiation, chemotherapy, or some combination thereof. Stage I-IIIA disease is primarily managed with surgery, whereas stage IIIB and IV disease is not. Because PET is hypothesized to discover occult metastatic disease, PET will most likely affect decisions whether or not to use surgery. As a result, this study will focus on treatment decisions with regards to surgery, chemotherapy, or radiation therapy, and no treatment (**Table 4.10**). CPT/HCPCS codes was used to identify resection, chemotherapy, and radiation therapy per Farjah et al. [9] Additionally, Medicare Durable Medical Equipment (DME) claims were examined for National Drug Codes (NDCs) that correspond to chemotherapy. Total health care costs was calculated by summing all line item Medicare claims from the inpatient, outpatient, and carrier files and adjusting for inflation to 2008 dollars using consumer pricing index.[79]

Table 4.10: Aim 3 dependent variables

Dependent Variables	Possible Values	Variable Type
Treatment	Resection, Other (Radio/Chemotherapy), None	Categorical
Total Health Care Claims	Dollars adjusted to 2008	Continous

The key independent variable was receipt of PET in the two months prior to or four months following diagnosis (Aim 2). Preliminary analyses confirmed that over 90% of PET scans were received within the first month or two of diagnosis and prior to or concomitant with

treatment within the Medicare-SEER data. Control variables were the same as those discussed in Aim 2.

4.5.3 Statistical Analyses

Using Medicare-SEER data, Aim 3 analyzed changes in stage-specific health care utilization and costs of lung cancer patients undergoing PET imaging between 1993-1994, 1998-1999 and 2004-2005 (**Figure 4.2**: dataset/population 3).

In hypothesis H3a1, I tested whether or not receipt of PET was associated with fewer surgeries. To do this I compared individuals receiving any PET vs. no PET within the subgroup of patients diagnosed in 1996-2005. Logistic regression was used to model whether or not PET affects the likelihood of an individual to receive surgery. The regression was modeled with and without controlling for cancer stage and its interaction with receipt of PET. Controlling for stage allowed me to examine whether individuals getting PET receive the same aggressiveness of treatment for the same stage cancer. Not controlling for stage examined overall rates of treatment. Overall thoracotomy rates were expected to decrease as a result of stage migration. I hypothesized that a shift in total thoracotomy rates would only be apparent when stage was not controlled for.

To test the hypothesis that PET was associated with an increased use of chemotherapy and radiation, a similar logistic regression tested whether or not a patient received *other treatment*, regardless of whether or not the patient underwent surgery:

$$\Pr(\textit{Treatment}) = f(\beta_0 + \beta_1 \text{PET} + \beta \text{ Controls})$$

Eq 3A

The frequency of patients undergoing surgery (resection), other treatment, and no treatment was compared between subgroups using chi-squared tests.

I tested the hypothesis that total 1-year Medicare payments (costs) were decreased in patient populations receiving PET due to avoidance of futile thoracotomies (hypothesis H3b1). Total 1-year Medicare payments were compared between individuals receiving PET and not receiving PET within the 2004-2005 (Post-PET) cohort, controlling for stage.

$$\text{Total Health Care Costs} = \beta_0 + \beta_1 \text{Year} + \beta_1 \text{PET} + \beta_1 \text{Stage} + \beta \text{ Controls} \qquad \text{Eq 3B}$$

One-year cost was compared in aggregate before and after the introduction of PET within groups adopting PET (high PET propensity) vs. those groups not adopting PET (low PET propensity). Each pre-PET subgroup (1993-1994, pre-PET; 1998-1999, initial-PET) was separately compared to the post-PET subgroup (2004-2005). PET is expected to reduce costs through the reduction of futile thoracotomies and related expenses.

Each cost analysis was performed both with and without controlling for the cumulative observation time (time to death, hospice, or managed care). Analyses using cumulative observation time will provide payments and treatment utilization per unit time. Additional sensitivity analyses controlled for SEER registry, limited analysis years to 1998-2003 to provide consistent stage definitions, and used an alternative 4 month minimum survival exclusion criteria. All regression analyses in Aim 3 was carried out using clustered errors (at the level of SEER registry) [81].

4.5.4 Expected Outcomes, Strengths, Limitations, and Alternative Methods

Successful completion of this aim sought to provide overall and stage-specific estimates of health care utilization and costs associated with the use of PET technology. Controlling for PET-induced stage migration and selection bias should provide a more accurate assessment of the actual costs and benefits of PET technology in the management of lung cancer in the Medicare patient population. Medicare-specific estimates of changes in survival, treatment, and costs associated with PET use in lung cancer will help inform future Medicare health policy decisions. I hypothesized that PET use would be associated with more aggressive stage-specific patient management and higher overall health care utilization and costs. However, overall health care utilization and costs may be decreased in populations using PET due to the ability to avoid unnecessary treatment.

Earlier detection of NSCLC using PET may increase the period of time during which a patient receives expensive therapy. Costs may be affected by the total time during which a patient submits claims through Medicare, which can be shortened to less than two years if a patient joins an HMO, dies, or enters hospice. The total time during which a patient is likely to file claims, or cumulative incidence function, was used to repeat cost analyses normalizing for the length of patient observation. Similar results were expected from both analyses. Each cost analysis was repeated controlling for observation length (cumulative incidence) to investigate this possibility.

I performed sensitivity analyses to confirm that cost analyses are not sensitive to the 2 year window used to assess costs: I repeated the analysis using costs accrued within varied window lengths (for example total costs within one year of diagnosis). I expected analysis results between the original and sensitivity analyses to yield qualitatively similar results over a range of cost receipt window lengths.

Aim 3 examines total patient claims, which included health care services performed for any reason among patients with a recent diagnosis of NSCLC and reflects costs in these patients incurred for both cancer and non-cancer related purposes. Patient prescription drugs or chemotherapy not administered by a physician are not captured in the Medicare data, which excludes oral prescription medications such as oral chemotherapy or supportive medications (e.g. medications for nausea or pain). Costs not covered by Medicare (aka deductibles or privately insured expenses) are not available in the Medicare data.

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CHAPTER 5: DEMOGRAPHIC AND REGIONAL VARIATION IN THE USE OF POSITRON EMISSION TOMOGRAPHY FROM 1998 TO 2005 IN THE MEDICARE NON-SMALL CELL LUNG CANCER POPULATION

ABSTRACT

Context:

The use of positron emission tomography (PET) increased rapidly among Medicare beneficiaries with non-small cell lung cancer (NSCLC) following its approval in 1998. Which demographic and regional subgroups were the recipients of this new technology and how its utilization changed over time is poorly understood. Understanding which patients had PET as part of their initial diagnostic evaluation is critical in order to determine the effect of PET on the clinical evaluation and management of NSCLC.

Objective:

To characterize changes in the receipt of PET within the Medicare NSCLC patient population between 1998 and 2005.

Design, Setting, and Patients:

Retrospective analysis of demographic, clinical, and claims data from Surveillance Epidemiology and End Results (SEER)-Medicare patients diagnosed with NSCLC between 1998 and 2005.

Main Outcome Measures:

Use of one or more PET scans as a function of patient factors among newly diagnosed cases of NSCLC between 1998 and 2005.

Results:

A total of 36,759 cases of NSCLC diagnosed between 1998 and 2005 met study criteria. By 2005, more than half of all NSCLC patients received one or more PET scans regardless of demographic subgroup. Ninety percent of patients received their initial PET scan concurrent with or prior to any treatment. Multivariable logistic regression of PET use between 1998 and 2005 suggested that patients who received PET were more likely to be married, be non-black, younger than age 81, and live in the Northeast (all $P<0.001$). Imaging rates increased more rapidly in patients who were non-black ($P\leq0.01$), younger than age 81, and lived in the Northeast and South compared with the Midwest and West ($P<0.001$).

Conclusion:

The use of PET imaging in the NSCLC Medicare patient population was initially concentrated among non-black patients younger than 81. Despite widespread adoption of PET among all subgroups, differences in overall PET utilization within sociodemographic and regional subgroups remained through 2005. How patterns of unequal PET dissemination have affected patient management, healthcare utilization, and outcomes remains an important area of future research.

5.1 Introduction

Positron Emission Tomography (PET) is an advanced imaging modality that began to be used to differentiate malignant and benign solitary pulmonary nodules in 1992[1] and was initially approved for this use by Medicare in 1998[2]. Since then, PET utilization has increased in clinical practice among both Medicare and privately-insured NSCLC patients[3,4]. By 2006, Medicare beneficiaries with lung cancer received an average of one PET scan per patient[3].

Previous studies suggest that the rapid expansion of PET may have occurred non-uniformly throughout the NSCLC patient population. Multimodality staging of NSCLC, which often includes PET, was more likely between 1998 and 2002 to be used in educated, higher income, white, married patients with early stage tumors[4]. Large regional variation in PET use has been documented: In 1998, the rate of PET use was 15 times higher in New York than Dallas, a difference that has persisted as late as 2007, albeit at a reduced level[5]. The observed regional differences may reflect general trends among Medicare beneficiaries undergoing diagnostic and imaging utilization[6].

Large, randomized clinical trials that evaluate the impact of PET on outcomes in NSCLC would be difficult to justify and financially prohibitive. Previous observational studies have reported an association between PET and superior NSCLC patient outcomes in Medicare beneficiaries[4] and one large privately insured California population[7]. However, such findings may be biased if PET is selectively administered to populations with greater access to health care. Understanding how this emerging technology is being used in the Medicare population and how its use has changed over time is critical to

understanding how PET utilization affects patient management, outcomes, and costs. Thus, we test the hypotheses that: (1) the initial adoption of PET among the Medicare NSCLC patient population was greater among younger, white, well-educated individuals living in wealthy communities and (2) this difference decreased as the use of PET became more widespread.

5.2 Methods

Data Source

Data are from the Surveillance Epidemiology and End Results (SEER)-Medicare linked data. SEER-Medicare is a collaborative effort between the National Cancer Institute (NCI) and Centers for Medicare and Medicaid Services (CMS) that links routinely-collected population-based data from cancer registries across the country to Medicare administrative data and health care claims. The SEER data provide demographic and incident cancer characteristics including grade, and stage for approximately 25% of the U.S. cancer population. Medicare provides health insurance for 97% of Americans aged 65 and older, and these data reflect health care services used and co-morbid health conditions present. SEER-Medicare data have been used previously to examine factors that affect cancer care quality including sociodemographics, physician and hospital characteristics, surgery, chemotherapy, radiation, comorbidities, complications, screening, relapse, and costs[8-18].

Study Population

All analyses were conducted using SEER-Medicare data from the 12 SEER registries that were continuously active from 1998 (the first year PET was approved for use for Medicare beneficiaries) onward. Within these registries, we included all patients who had a diagnoses of cancer of the lung and bronchus with microscopically confirmed NSCLC histology between 1998 and 2005, were age $\geq$ 66 years at diagnosis, and had Medicare Part A & B coverage without participating in a Health Maintenance Organization (HMO) or Medicare Part C for the year prior to and following their diagnosis or until death. We excluded patients who were diagnosed at autopsy or death, or had another diagnosis of malignancy in the year prior to their NSCLC diagnosis. We excluded patients who did not survive at least 2 months from diagnosis to exclude clinically morbid patients for whom we expected factors associated with PET use would be significantly different compared to the general population. To help ensure full acquisition of claims for cancer-related claims, patients were required to have a primary diagnosis of lung cancer on an inpatient, outpatient, or carrier-based Medicare claim (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* diagnosis of lung cancer [162.2-162.9, 231.2]).

Study Variables

The primary dependent variable was receipt of one or more PET scans within two months prior to, or four months after, NSCLC diagnosis. Receipt of PET scans was

detected using the following Healthcare Common Procedure Coding System codes within the Medicare outpatient and carrier files: G0125, G0126, G0163, G0164, G0165, G0235, G0252, G0253, G0254, G0296, G0330, G0331, 78810-78816, G0210-G0228, G0231-G0234, G0213-G0215, G0226-G0228[3]. Receipt of PET was considered to be concurrent with, or prior to, treatment if it occurred prior to or during the first month for which a surgical, radiation therapy, or chemotherapy claim was reported [9]. Distance to PET was modeled as a dichotomous variable (>40 miles vs. <= 40 miles) to define groups with maximally different PET use based on preliminary analyses and was based on previous literature demonstrating differential treatment of patients located >40 miles from treatment facilities[19]. We used inpatient, outpatient, and carrier Medicare claims records to calculate the National Cancer Institute (NCI) comorbidity index[20]. Patients were categorized as having zero, one, or more than one comorbidity.

All remaining variables were obtained from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF). Demographic variables included age, sex, race, ethnicity, marital status, and local census tract characteristics (metropolitan urban or rural status; percent not-finishing high school; percentage below the poverty line; and percent black). Histology of NSCLC was classified as either adenocarcinoma, large cell carcinoma, squamous cell, or NSCLC otherwise undifferentiated using the ICD-O-3 (*International Classification of Disease in Oncology 3rd Edition*) code on SEER diagnosis. Therapies undergone by patients within 4 months of diagnosis included surgery, chemotherapy, and radiotherapy. The 12 SEER registries included in the study were grouped according to their census regions: Northeast (Connecticut), Midwest

(Detroit, Iowa), South (Atlanta, Rural Georgia), and West (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles).

Statistical Analysis

PET use was stratified using categorical specifications of all analyzed variables. Patients were classified into early (1998-1999), middle (2001-2002), or late (2004-2005) cohorts to provide analysis of distinct phases of PET adoption. This classification was used to compare baseline characteristics of all NSCLC cases over time using chi-square tests. The proportion of patients receiving one or more PET scans as a function of subgroup and year of diagnosis were plotted to observe changes in PET use over time.

To address endogeneity, all models excluded variables that could potentially be affected by receipt of PET (e.g., disease stage, treatment decisions, overall survival). In all models, we present odds ratios (OR) and 95% confidence intervals (CI). The association between receipt of PET and patient characteristics was examined with a multivariable logit and linear probability model (LPM). In a second linear probability model, patient characteristics were interacted with year of diagnosis, to explore how the association between receipt of PET and patient characteristics changed over time as PET availability increased. An LPM was used instead of a logit model to examine the interaction between patient characteristics and year, since interaction terms within logit models differ by observation and are not amenable to generalized interpretation.[21] Errors were clustered by SEER registry for all regressions[22]. Two separate sensitivity analyses

of PET receipt were performed by 1) expanding the window for PET to one year following diagnosis and 2) controlling for SEER registry.

5.3 Results

Study Population

We identified 128,006 Medicare beneficiaries diagnosed with one or more cases of cancer of the lung and bronchus in the SEER registries between 1998 and 2005; among these patients, a total of 129,241 separate diagnoses of incident lung cancer were identified (some patients had two separate cases of primary lung cancer separated by over a year during the study period). We sequentially excluded patients (**Figure 5.1**) who were diagnosed at death or autopsy, were younger than 66 years of age, did not have microscopically-confirmed NSCLC histology, had another malignancy in the year before or after their diagnosis, participated in an HMO or did not have part A and part B coverage for the year before and after their diagnosis, did not survive a minimum of 2 months from their diagnosis, did not have an undocumented prior malignancy, and had to have a Medicare claims-based ICD-9 diagnosis of lung cancer within two months prior to and four months following SEER diagnosis. The final cohort consisted of 36,759 NSCLC cases.

Baseline Patient Characteristics by Early, Middle, and Late PET Adoption Cohorts

Baseline characteristics differed among NSCLC patients by early (1998-1999), middle (2001-2002), and late (2004-2005) PET adoption cohorts (**Table 5.1**). The diffusion of this innovative imaging technology into practice was evident in the consistently increasing proportion of beneficiaries who received at least one scan PET scan during the period from two months before, until four months after, diagnosis: 7.5% in 1998-1999; 30.8% in 2001-2002; and 51.5% in 2004-2005 (P<0.0001). The initial PET scan occurred either concurrently with, or prior to, treatment in over 90% of patients across all years. Compared with patients diagnosed during the later cohorts, patients diagnosed during earlier cohorts had to travel farther to reach the nearest PET facility, were younger, more frequently male, were more likely to be married, had fewer comorbidities, and came from census tracts with less education (All $P < 0.001$).

Comparison of PET-Receiving Patients in Late vs. Early Cohorts

To compare differences between the early and late adoption of PET, we compared characteristics of patients who received PET during the earliest vs. latest cohorts of NSCLC patients. Univariate comparisons (**Table 5.2**) revealed that, compared to the late cohort, the patient population who received PET in the early cohort had half as many individuals older than age 80 (11% vs. 20%), more patients without any comorbidities (60% vs. 50%), and almost half as many individuals from census tracts within the top quartile of percent black composition (13% vs. 22%). Between 1998 and 2005 there was a regional shift in PET use, with a doubling of the proportion of patients in our sample coming from the Northeast (18% vs. less than 9%), a several-fold increase in patients

from the South, and an 8% absolute decrease in patients from the Midwest (38% vs. 30%; all $P<0.001$).

Characteristics Associated With Receipt of PET in Late vs. Early Cohorts

Despite shifts in the relative composition of patients receiving PET, all subgroups experienced large increases in PET use over the study period, with at least half of all patients receiving PET by 2005 regardless of race, region, age, or local sociodemographic factors (**Figures 5.2A and 5.2B**). Despite widespread adoption of PET overall, patients older than age 80, blacks, and individuals from less educated or more impoverished census tracts had lower utilization of PET that persisted through 2005. PET use increased preferentially in the Northeast beginning in 2001, following the Medicare coverage expansion of PET for the diagnosis, staging, and re-staging of NSCLC. Patients living more than 40 miles from the closest PET providing facility had lower PET utilization during the first half of the study period, but exhibited equal use of PET by 2005.

Multivariable logistic regression using both a logit and LPM model (**Table 5.3**, Model 1) of PET use between 1998 and 2005 using suggested that patients who received PET were more likely to be married, female, non-black, under the age of 80, come from non-impoverished census tracts, and live in the Northeast (all $P\leq0.01$). To examine how patient characteristics associated with PET changed over time, we modeled the interaction between patient characteristics and year of diagnosis within the LPM model (**Table 5.3**, Model 2). Imaging rates increased more rapidly among patients who were

married, non-black, under age 81, and lived in the Northeast and South compared with the Midwest and West ($P \leq 0.01$). With each increasing year, PET utilization in patients over age 80 lagged an additional 1.2 percentage points behind younger patients. Black patients lagged an additional 0.8 percentage points behind non-blacks with each increasing calendar year of diagnosis. Patients with a single comorbidity were more likely to receive a PET scan during later years of the study.

Sensitivity analyses were conducted using PET scans performed within 12 months prior to and following NSCLC diagnosis, in addition to the initial definition. Overall rates of PET use increased by roughly 10% using this method, but did not qualitatively change these analysis results. Regressions run including SEER registry as a control did not qualitatively affect the analysis results.

5.4 Discussion

PET utilization among NSCLC patients increased following its approval by Medicare in 1998, reaching a utilization rate of 50% or more by 2005 regardless of race, age, region, or local census characteristics. Despite widespread adoption of PET overall, patients who were older, black, or from less educated or more impoverished census tracts had lower utilization of PET that persisted through 2005, with an absolute deficit in PET utilization of approximately ten percentage points within each group. Expansion of PET occurred preferentially within the Northeast following Medicare expansion of PET indications for the diagnosis, staging, and restaging of NSCLC in 2001. Although we initially hypothesized that the unequal utilization of PET would decrease with increasing

PET availability, we found that differences in absolute utilization rates increased among subgroups based on race, age, marital status, and region through 2005.

Heterogeneous spread of PET use may increase as new guidelines and approved uses emerge. On July 1 2001, PET was approved for the diagnosis, initial staging, and restaging of NSCLC. This national coverage determination should in theory have equally affected the adoption of PET use in NSCLC nationwide. However, between 2001 and 2002, the Northeast (Connecticut) registry increased its use of PET significantly faster than all other registries. It has been previously shown that the introduction of new technology often occurs heterogeneously during the early phases of growth [23 5 24]. Our results suggest that issuing national coverage determination may also introduce a potential source of increased heterogeneous use of existing technology.

Possible explanations for disparate use of PET include differences in the availability of technology, cost, physician preference, and patient preference. PET scanners are expensive resources that may not be available at disadvantaged hospitals. PET was initially approved for use in early stage, or as yet undiagnosed lung cancer. Patients that typically present with NSCLC at later stages of disease, such as those in disadvantaged socioeconomic areas, might be less likely to receive PET as a result. The direct relationship between receipt of PET and stage is complicated, as both PET and stage can causally affect each other. Disparities in race, gender, and age have been observed with regards to cancer health care access, treatment, and survival [25-43], particularly with regards to receiving new or higher-technology services [26]. African Americans and whites are often treated at different hospitals [31], with hospitals that treat

large proportions of African American patients being less likely to perform emerging medical procedures on any of their patients [25].

Whether or not PET improves outcomes or reduces costs is unclear. Potential benefits include earlier diagnosis, more accurate staging, and avoidance of unnecessary, aggressive treatments such as thoracotomy in the setting of metastatic disease. Small randomized controlled trials have suggested that PET can alter management decisions in as many as one-third of newly-diagnosed NSCLC patients [44]. Larger randomized controlled trials are lacking, and epidemiologic studies have shown mixed results. A study by Farjah et al. suggested that PET use was associated with decreased mortality [4]. However, such findings must be interpreted cautiously given the clear heterogeneity of adoption of PET in the Medicare population, selection bias, and the potential for stage migration and the accompanying Will Roger's phenomena [45], in which upstaging disease appears to improve stage-specific survival. Among NSCLC SEER-Medicare patients with advanced stage disease, blacks fared worse than whites from 2000-2002 period, but not earlier periods[40]. The differential adoption of emerging medical technology has previously been implicated in introducing such disparities in cancer management and outcomes[46]. Regardless of the true benefit of PET, this study demonstrates that PET use did not spread equitably within the Medicare NSCLC patient population and that this unintended discrepancy in care persisted despite high overall uptake.

This study has several limitations as a retrospective, claims-based analysis. First, only PET scans paid for by Medicare could be detected in our analysis. However, it is likely that relatively few PET scans for our sample of Medicare beneficiaries would be paid by third party insurers or out of pocket. Second, it is unknown how reliable

Medicare claims data are for determining receipt of PET. However, studies examining the accuracy of Medicare claims for assessing alternative imaging modalities such as mammography have had observed concordance rates of 94% [47]. How reliable Medicare claims data are for determining the receipt of PET or other advanced imaging modalities may be a potential area of future investigation. Third, patients within the SEER registry are overall more likely to be non-white, live in non-poverty areas, and live in urban areas[22], which may limit the ability to generalize our findings. Fourth, we did not incorporate patient stage, treatment decisions, survival, or other factors that could themselves altered by receipt of PET. Finally, SEER-Medicare data are released with a several year lag, limiting the ability of the analysis to extend beyond 2005 at the time of the study.

Advanced imaging studies such as PET, computed tomography, and magnetic resonance imaging represent some of the fastest growing areas of resource utilization within the Medicare cancer population. We found that differences in utilization within sociodemographic and regional subgroups remained through 2005. In this study, we examined only the first PET scan administered to patients. Future areas of research may include the use of multiple PET scans in the same individuals, the timing and purpose of follow-up scans, and longer term monitoring. The role of access to PET providing facilities and providers may also grant insight into how PET has spread from a health systems perspective. Although we found differential utilization rates among specified subgroups, it is unclear as to whether this represents relative under-utilization vs. over-utilization. The input of unequal adoption of PET on patient care, outcomes, and costs remain an important area of current and future health policy research.

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This study was approved by the Office of Human Research Ethics at the University of North Carolina, Chapel Hill. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary NC).

Table 5.1: Baseline demographic characteristics of all NSCLC cases by year of diagnosis (early – 1998-1999/ middle - 2001-2002/ late - 2004-2005)

Characteristic	Year of Diagnosis				*P* Value[a]
	Early Cohort 1998-1999 (n = 8,939)	Middle Cohort 2001-2002 (n = 9,367)	Late Cohort 2004-2005 (n = 10,436)	Overall 1998-2005 (n = 36,759)	
Any PET scans, No. (%)	380 (4.7)	3062 (32.7)	6303 (60.4)	12811 (34.9)	<.0001
Distance to PET <= 40 miles, No. (%)	4845 (60.4)	8257 (88.2)	9739 (93.3)	30544 (83.1)	<.0001
Age > 80, No. (%)	1460 (18.2)	1965 (21)	2342 (22.4)	7576 (20.6)	<.0001
Male, No. (%)	4416 (55.1)	4947 (52.8)	5312 (50.9)	19459 (52.9)	<.0001
Race, No. (%)					0.004
Caucasian/Other	8269 (92.5)	8618 (92.0)	9574 (91.7)	33794 (91.9)	
Black	670 (8.4)	749 (8)	862 (8.3)	2965 (8.1)	
Comorbid conditions, No. (%)					<.0001
0	4514 (56.3)	4939 (52.7)	5186 (49.7)	19304 (52.5)	
1	2185 (27.3)	2676 (28.6)	3071 (29.4)	10512 (28.6)	
2+	1318 (16.4)	1752 (18.7)	2179 (20.9)	6943 (18.9)	
Census tract characteristics: (Highest Quartile)					
Did not complete high school	1714 (26.3)	2005 (24.8)	2163 (23.3)	7782 (24.7)	0.0001
Percent below poverty line	1721 (26.4)	1986 (24.6)	2177 (23.5)	7725 (24.5)	0.0002
Percent black	1633 (25)	1992 (24.7)	2252 (24.3)	7734 (24.5)	0.57
Married (%)	4533 (56.5)	5036 (53.8)	5496 (52.7)	19883 (54.1)	<.0001
Metropolitan (%)	6819 (85.1)	8041 (85.8)	8977 (86)	31452 (85.6)	0.02
Any Therapy (%)	6791 (84.7)	7916 (84.5)	8755 (83.9)	30964 (84.2)	0.03
Histology					<.0001
Adenocarcinoma	3890 (48.5)	3791 (40.5)	4371 (41.9)	16051 (43.7)	
Large Cell	876 (10.9)	683 (7.3)	575 (5.5)	306 (7.7)	
Other*	395(4.9)	2218 (23.7)	2820 (27.0)	341 (18.9)	
Squamous Cell	2856 (35.6)	2675 (28.6)	2670 (25.6)	564 (29.7)	
Region					0.0004
West	3464 (43.2)	4173 (44.6)	4749 (45.5)	16281 (44.3)	
Midwest	2847 (35.5)	3116 (33.3)	3376 (32.4)	12418 (33.8)	
Northeast	1156 (14.4)	1455 (15.5)	1626 (15.6)	5642 (15.3)	
South	550 (6.9)	623 (6.7)	685 (6.6)	2418 (6.6)	

[a] Chi-Squared test for association with cohort.

* Composed of adenosquamous, carcinoid, carcinoid with mesenchymal features, salivary, and unclassified histologies.

NSCLC: non-small cell lung cancer; PET: positron emission tomography.

Table 5.2: Univariate comparison of NSCLC patients receiving PET during the early (1998-1999) vs. late (2004-2005) phases of PET adoption

Characteristic	Patients Receiving One or More PET Scans		
	Early (1998-1999) (N = 380)	Late (2004-2005) (N = 6,303)	*P* Value [a]
Miles to PET ≤ 40, No. (%)	319 (84)	5915 (93.8)	<.0001
Age > 80, No. (%)	40 (10.5)	1241 (19.7)	<.0001
Male, No. (%)	210 (55.3)	3185 (50.5)	0.07
Race, No. (%)			0.25
Caucasian/Other	364 (95.8)	5893 (93.5)	
Black	16 (4.2)	410 (6.5)	
Comorbid conditions, No. (%)			0.001
0	226 (59.5)	3142 (49.9)	
1	97 (25.5)	1880 (29.8)	
2+	57 (15)	1281 (20.3)	
Census tract characteristics: (Highest Quartile)			
Did not complete high school	49 (16.1)	1133 (20.3)	0.08
Percent below poverty line	59 (19.4)	1138 (20.4)	0.68
Percent black	38 (12.5)	1247 (22.3)	<.0001
Married (%)	243 (64)	3470 (55.1)	0.0007
Metropolitan (%)	340 (89.5)	5446 (86.4)	0.09
Any Therapy (%)	348 (91.6)	5600 (88.9)	0.10
Histology			<.0001
Adenocarcinoma	215 (56.6)	2682 (42.6)	
Large Cell	24 (6.3)	297 (4.7)	
Other*	21 (5.5)	1646 (26.1)	
Squamous Cell	120 (31.6)	1678 (26.6)	
Region			<.0001
West	202 (53.2)	2873 (45.6)	
Midwest	144 (37.9)	1873 (29.7)	
Northeast	†34 (<8.9)	1133 (18)	
South	†34 (<8.9)	424 (6.7)	

[a] Chi-Squared test for association with cohort.

* Composed of adenosquamous, carcinoid, carcinoid with mesenchymal features, salivary, and unclassified histologies

†Northeast and South Categories have been combined for the 1998-1999 cohort to suppress cell sizes <11.

NSCLC: non-small cell lung cancer; PET: positron emission tomography.

Table 5.3: Multivariable logistic regression comparing NSCLC patients receiving one or more PET scans vs. patients receiving no PET scans

Characteristic	Logit Model		Linear Probability Model		
	Model 1 Overall PET Use		Model 1 Overall PET Use	Model 2 Changes over time	
	Coefficent	OR (95% CI)	Coefficient	Base Coefficent	Intxn w/ Year Coef. †
Miles to PET > 40	-0.56**	0.57 (0.45-0.73)	-4.4	-1.4	-1.3
Age > 80	-0.43**	0.65 (0.61-0.69)	-7.6**	-2.7*	-1.2**
Black	-0.35**	0.71 (0.67-0.74)	-5.6**	-2.7*	-0.8*
Comorbidity					
One	0.06	1.06 (0.99-1.14)	1.1	-0.8	0.5**
Multiple	0.03	1.03 (0.97-1.09)	0.4	-0.9	0.3
Census tract: % Education < 12 years					
2nd QRTL	-0.19	0.83 (0.71-0.97)	-3.5	-4.5	0.3
3rd QRTL	-0.31*	0.73 (0.58-0.93)	-5.7	-6.1	0.1
4th QRTL	-0.48*	0.62 (0.45-0.86)	-8.3*	-6.4	-0.5
Census tract: % below poverty line					
2nd QRTL	0.06	1.06 (0.92-1.22)	1.1	1.2	0
3rd QRTL	0.10	1.11 (0.96-1.28)	1.6	3.3	-0.4
4th QRTL	-0.02	0.98 (0.83-1.16)	-0.7	2.6	-0.8
Census tract: % Black					
2nd QRTL	0.03	1.03 (0.90-1.18)	0.7	-0.5	0.3
3rd QRTL	0.11	1.11 (0.93-1.33)	2.2	0.7	0.3
4th QRTL	0.01	1.01 (0.86-1.20)	0.6	-0.3	0.2
Male	-0.09*	0.92 (0.87-0.97)	-1.6**	-0.7	-0.2
Married (%)	0.15**	1.16 (1.11-1.22)	2.7**	0.7	0.5*
Metropolitan (%)	-0.13	0.87 (0.76-1.01)	-0.2	2.7	-0.9
Region					
West	0.27	1.31 (1.01-1.71)	4.5	1	1
Northeast	0.47**	1.60 (1.36-1.90)	8.7**	-3.1	3**
South	-0.02	0.98 (0.82-1.19)	-0.2	-8.2**	2**
Year	0.50**	1.65 (1.55-1.77)	9.2**	10.6**	

*P≤.01, **P ≤.001. OR: Odds Ratio; CI: Confidence Interval; NSCLC: non-small cell lung cancer; PET: positron emission tomography; QRTL: Quartile; Intxn: Interaction; Coef: Coefficient

†Model 2 included an interaction term between each patient characteristic in model 1 and the year of diagnosis, with 1998 used as the reference category. Interaction coefficients represent the additional association of a patient characteristic w/ PET use for each year after 1998.

Figure 5.1: CONSORT Diagram of Study Inclusion/Exclusion Criteria

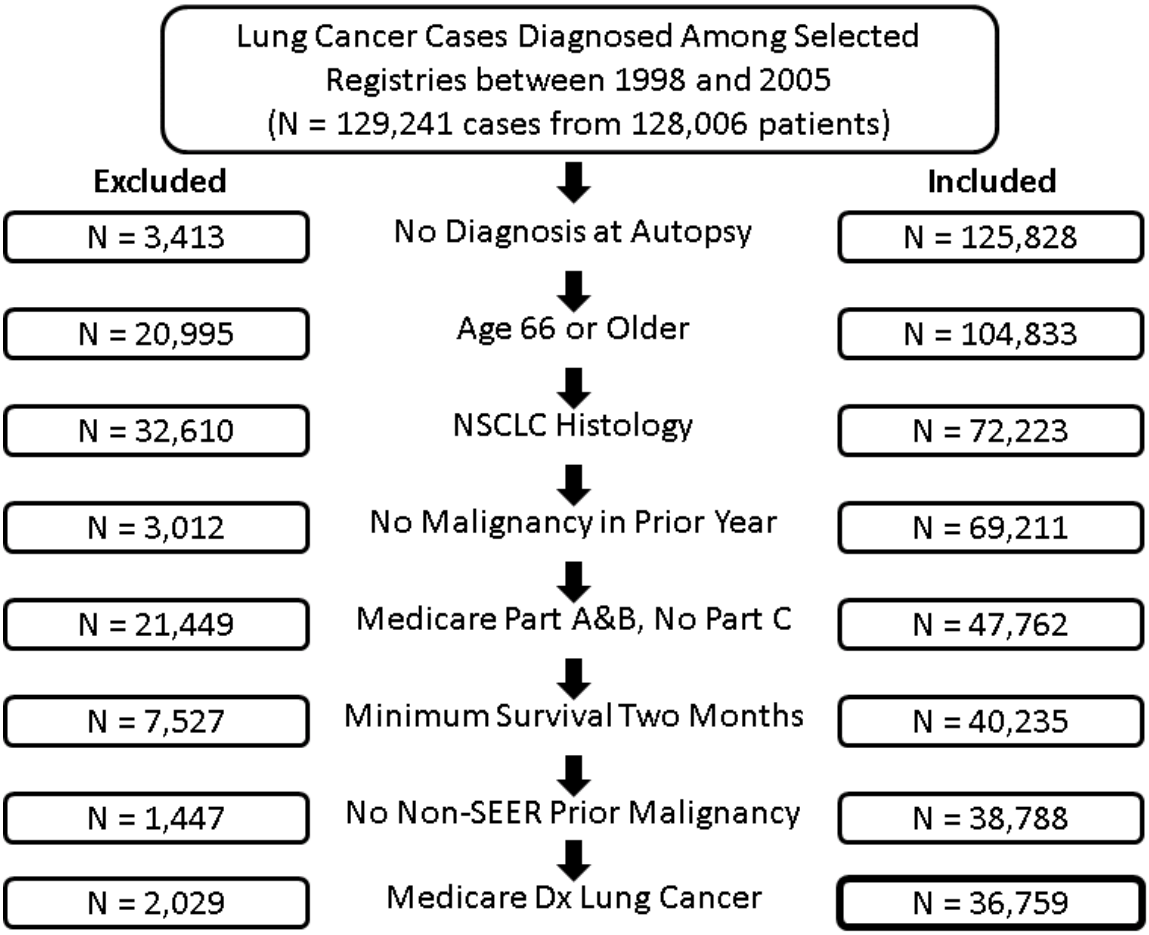
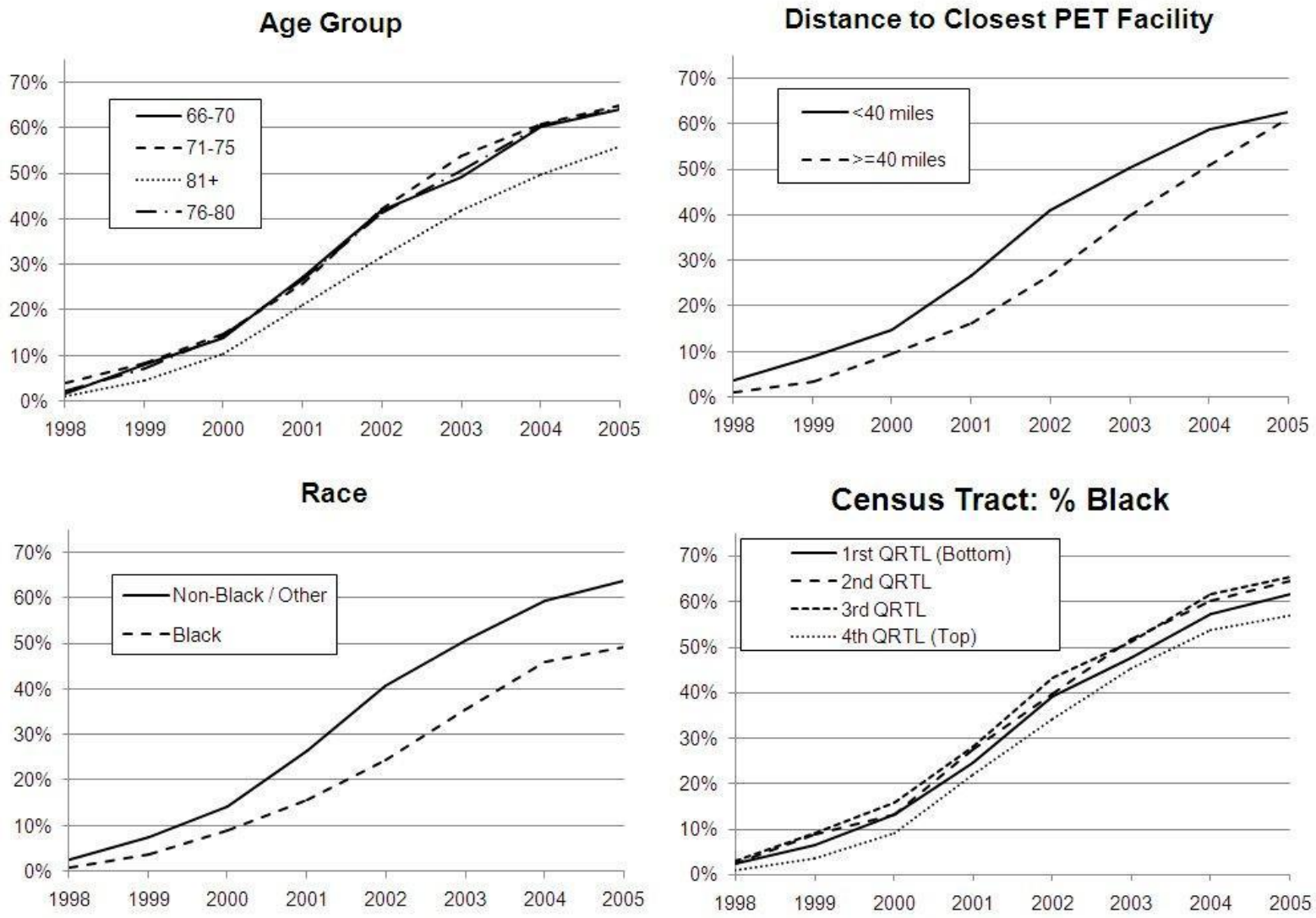
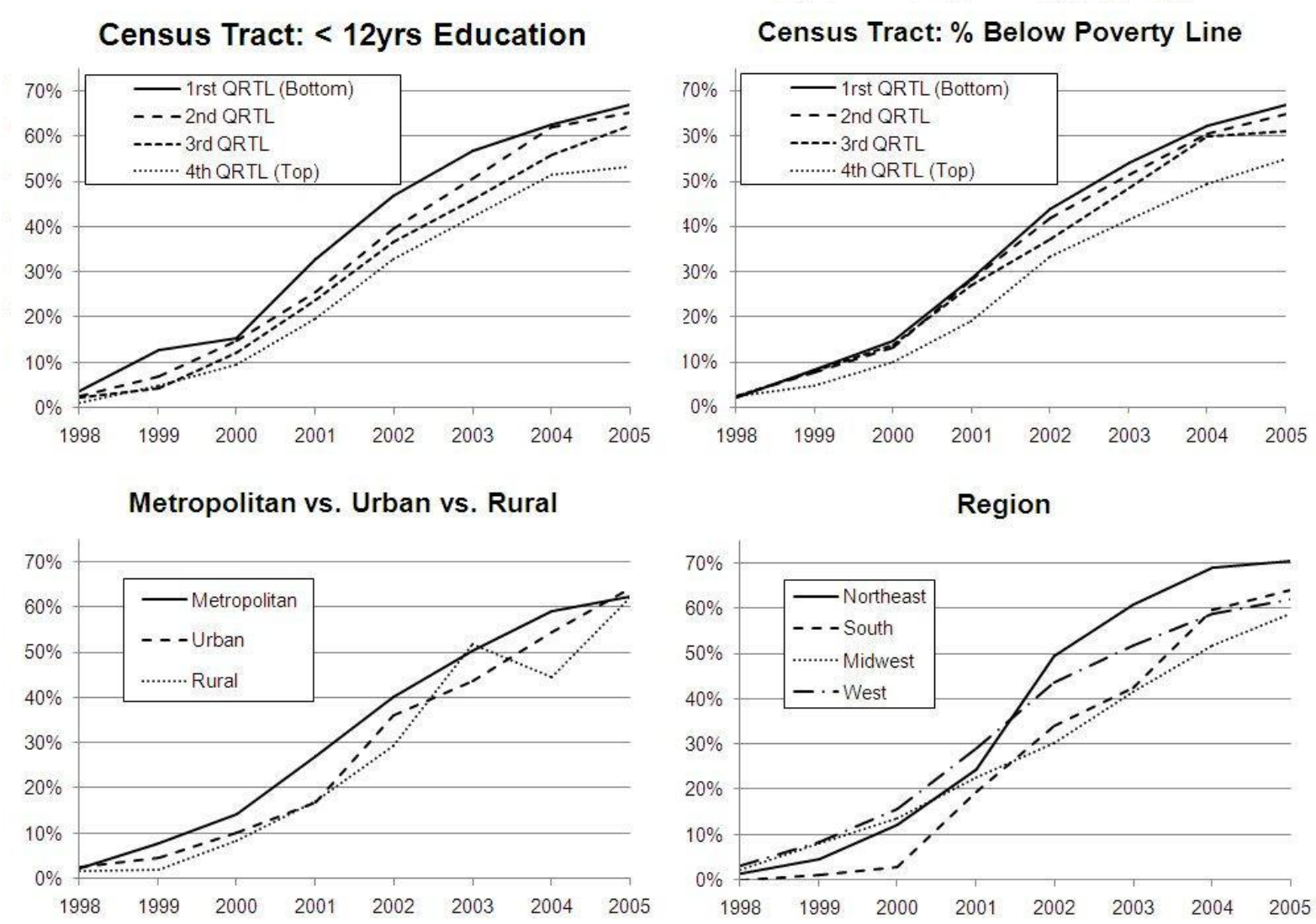


Figure 5.2A: Proportion of NSCLC Patients Receiving One or More PET Scans by Subgroup and Year of Diagnosis from 1998-2005.



QRTL: Quartile

Figure 5.2B: Proportion of NSCLC Patients Receiving One or More PET Scans by Subgroup and Year of Diagnosis from 1998-2005.



QRTL: Quartile

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CHAPTER 6: PET-INDUCED STAGE MIGRATION AND SELECTION BIAS FROM 1998 TO 2005 IN THE MEDICARE NON-SMALL CELL LUNG CANCER POPULATION

Context:

The use of Positron Emission Tomography (PET) spread rapidly among the Medicare lung cancer patient population following its approval in 1998. Previous studies have suggested that increasing PET use may be associated with improved outcomes in non-small cell lung cancer (NSCLC). However, this association may be complicated by PET-induced stage migration and selection bias. How PET affects the staging, management, and outcomes of NSCLC patients remains an important question in the Medicare NSCLC patient population.

Objective:

To examine the association between PET use and overall survival in the Medicare beneficiaries with NSCLC, controlling for PET-induced stage migration and selection bias.

Design, Setting, and Patients:

Retrospective analysis of SEER-Medicare data to characterize changes in overall survival, stage-specific survival, and stage distribution within the Medicare NSCLC patient population between 1998 and 2005.

Main Outcome Measures:

Two-year overall survival, stage-specific survival, and stage distribution.

Results:

A total of 207,291 cases of NSCLC diagnosed between 1993 and 2005 met study criteria. By 2005, 62% of patients diagnosed with NSCLC received one or more PET scans, compared with

only 4% in 1998. Overall two-year survival among the Medicare NSCLC population increased less than two percentage points between 1998 and 2005, despite the widespread adoption of PET. The total proportion of patients staged with advanced, or stage IIIB/IV, disease increased from 40% to 50% between 1998 and 2005. Upstaging of disease was accompanied by stage-specific improved survival, with two-year survival of advanced disease increasing from 10% to 16% between 1998 and 2005. PET was more likely to be administered to patients with less advanced disease and greater overall two-year survival.

Conclusion:

Overall survival of Medicare NSCLC patients increased by less than two percentage points between 1998 and 2005, despite the widespread adoption of PET. The introduction of PET coincided with substantial stage migration among Medicare NSCLC patients, with a concomitant increase in advanced stage disease and decrease in unstaged disease. The frequent use of PET among NSCLC patients with less advanced disease appears to account for previously observed associations between receipt of PET and a two-fold increased rate of survival. The increased use of PET in the Medicare NSCLC patient population and how it affects patient management and health care utilization remains an important area of ongoing research and evolving health policy.

6.1 Introduction

Positron Emission Tomography (PET) is an advanced imaging modality used in the clinical diagnosis, staging, and restaging of non-small cell lung cancer (NSCLC) patients. The use of PET in NSCLC was initially approved by Medicare in 1998[1] and has since increased rapidly in both Medicare and privately-insured lung cancer patients[2,3].

The use of PET, particularly in conjunction with dedicated dual PET/CT scanners, provides more sensitive detection of occult metastatic NSCLC compared with CT alone.[4-6] However, it is unclear whether or not the use of PET affects patient outcomes, particularly survival. To date, there have been only four RCTs examining the use of PET in NSCLC. These trials have consistently demonstrated PET-induced upstaging of disease due to PET's ability to detect occult metastatic spread, but have not been powered to detect a change in patient survival. [7-10]

Previous observational studies have reported an association between PET and improved NSCLC patient outcomes.[3,11] However, such findings may be biased if PET is selectively administered to populations with greater access to health care. PET is a more sensitive method of detecting extent of disease than conventional staging technologies. It is typically used in conjunction with older technology such as computed tomography (CT). PET scans are recommended for patients with early stage disease, specifically to rule out the presence of occult metastatic disease prior to surgery.[4] Because PET is used in addition to conventional CT or other staging modalities, the application of PET to a population can result in higher tumor stages being assigned to biologically equivalent cancers, a phenomenon known as stage migration (**Figure 6.1**). A known effect of stage migration is that stage-specific survival outcomes may appear improved in the absence of any actual patient benefit. This phenomena is particularly

germane because an epidemiologic study of one large private California insurer[12] and three out of four small randomized controlled trials (RCTs)[7-10] have suggested that PET may result in upstaging of occult metastatic NSCLC from early to late stage disease [12].

A previous study of Medicare beneficiaries with NSCLC found a two-fold increased association between PET and overall survival[3]. Limitations of the study included possible selective administration of PET to patients with less advanced disease and stage migration. In this study, we seek to understand how PET is associated with the outcomes of Medicare beneficiaries with NSCLC. Specifically, we test the hypothesis that adoption of PET among Medicare beneficiaries with NSCLC was associated with upstaging and detection of occult metastatic disease, improvement in stage-specific survival, and no change in overall survival.

6.2 Methods

Data Source

Data are from the Surveillance Epidemiology and End Results (SEER)-Medicare linked data. SEER-Medicare is a collaborative effort between the National Cancer Institute (NCI) and Centers for Medicare and Medicaid Services (CMS) that links routinely-collected population-based data from cancer registries across the country to Medicare administrative data and health care claims. The SEER data include demographic and incident cancer characteristics including grade, and stage for approximately 25% of the U.S. cancer population. Medicare provides health insurance for 97% of Americans aged 65 and older, and these data reflect health care services used and co-morbid health conditions. SEER-Medicare data have been used previously to examine factors that affect cancer care quality including sociodemographics, physician and

hospital characteristics, surgery, chemotherapy, radiation, comorbidities, complications, screening, relapse, and costs[13-23]. This study was approved by the Office of Human Research Ethics at the University of North Carolina, Chapel Hill.

Study Population

All analyses were conducted using SEER-Medicare data from the 12 SEER registries that were continuously active from 1998 (the first year PET was approved for use for Medicare beneficiaries) onward. Within these registries, we included all patients who had a diagnoses of cancer of the lung and bronchus with microscopically confirmed NSCLC histology between 1998 and 2005, were $\geq$ 66 years at diagnosis, and had Medicare Part A & B coverage without participating in a Health Maintenance Organization (HMO) or Medicare Part C for the year prior to and following their diagnosis or until death. We excluded patients who were diagnosed at autopsy or death, or had another diagnosis of malignancy in the year prior to their NSCLC diagnosis. We excluded patients who did not survive at least 2 months from diagnosis to exclude patients with poor performance status for whom PET administration was thought to be unlikely. To identify patients likely to have complete Medicare claims related to their NSCLC management, patients were required to have a primary diagnosis of lung cancer on an inpatient, outpatient, or carrier-based Medicare claim (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* diagnosis of lung cancer [162.2-162.9, 231.2]).

Study Variables

The primary outcomes were stage at diagnosis and survival at two years. Cancer stage was ascertained from SEER data and extrapolated to the staging system used by the American Joint Committee on Cancer (AJCC) 3rd edition to provide a common staging system throughout the study period. [24] Within the SEER data, patients diagnosed prior to 2003 are staged using the AJCC 3rd edition, while patients diagnosed in 2004 and later are staged using the AJCC 6th edition. To provide consistent 3rd edition staging, we converted the 6th edition staged cancers to the 3rd edition by reverting the staging of T3N0 tumors from IIB to IIIA, collapsing stage IA and IB into stage I, and collapsing stage IIA and IIB into stage II. Alternative staging systems available within SEER were investigated for trends in stage migration including SEER-modified AJCC 3rd edition (available 1993-2003), SEER summary staging, and the SEER historic staging. [25] Survival at two years was obtained from SEER date of death. We chose to evaluate survival at two years to provide a clinically meaningful endpoint that would also allow us to be able to detect changes in survival across all disease stages, which ranges between 5% to 75% as a function of stage.[26]

Receipt of PET was detected using outpatient and carrier claims in the period two months prior to, and four months following SEER diagnosis to coincide with the 4-month period used by SEER to provide cancer stage from 1998 onward[27]. To control for patient access to PET, we extracted all PET claims from 1993 to 2005 to identify all outpatient facility providers and universal physician identification numbers (UPINs) associated with a PET claim during the study period. A patient was defined as having accessed a PET provider or outpatient facility if he or she had any claims from a facility, provider, or referring provider that had previously offered a PET scan within the study population. Histograms of the total number of PET-scanned patients per facility and provider were generated to assess PET access patterns. SEER-based patient zip codes and Medicare carrier

claim zip codes were used to determine the straight-line distance between patients and the closest location of PET administration at the time of diagnosis. [28,29]

All remaining variables were obtained from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF). Demographic variables included age, sex, race, ethnicity, marital status, and local census tract characteristics (metropolitan urban or rural status; percent not-finishing high school; percent below the poverty line; and percent black). Histology of NSCLC was classified as adenocarcinoma, large cell carcinoma, squamous cell, or NSCLC otherwise undifferentiated using the ICD-O-3 (International Classification of Disease in Oncology 3rd Edition) code on SEER diagnosis. Antineoplastic interventions delivered within 4 months of diagnosis were categorized as surgery, chemotherapy, or radiotherapy. The 12 SEER registries included in the study were grouped according to their census regions: Northeast (Connecticut), Midwest (Detroit, Iowa), South (Atlanta, Rural Georgia), and West (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles).

Statistical Analysis

As with the initial report of technology-induced stage migration in lung cancer[30], we used categorical specifications of study variables because they change more predictably than group averages or medians as members of one group migrate to another. To study change in staging and survival over time, patients were grouped by year of NSCLC diagnosis into cohorts representing the pre-PET (1993-1994), initial-PET (1998-1999), and post-PET (2004-2005) phases of PET adoption observed in previous work.[31] Baseline patient characteristics of all NSCLC cases between the pre-, initial, and post-PET cohorts were compared using chi-squared tests to assess general differences in the Medicare NSCLC population over the study period.

Two-year periods representing distinct phases of PET adoption were chosen to provide discrete assessments of the effect of PET at specific phases in the use of PET.

Overall trends in stage distribution and survival were plotted by year of diagnosis from 1993 through 2005 among the overall Medicare NSCLC population and by age group, race, number of comorbidities, and region. Advanced disease was defined as stage IIIB or IV, which corresponds clinically to incurable disease.

We employed multivariable logistic regression and univariate comparisons to analyze the association of PET with stage migration and survival. Multivariable logistic regression was performed using three separate regression models. All models included patients diagnosed between 1996 and 2005 for whom 2000 census demographic variables were available. Model 1 analyzed the likelihood of stage IV disease as a function of receipt of PET, controlling for patient demographics including year of diagnosis, age, race, sex, marital status, residence in a metropolitan area, and region as well as census tract-based levels of local education, income, and demographic composition. To control for access to PET, we included whether or not patients received any of their care at a PET providing physician or facility. Survival was modeled at two years as a function of PET and the same control variables. This survival analysis was performed both excluding (model 2) and including (model 3) cancer stage as well as its interaction with PET to assist in interpreting the regression results in the setting of suspected PET-induced stage migration.

As an additional sensitivity analysis for our regression models, we attempted to mitigate selection bias by matching the propensity of patients to receive a PET scan based on available demographics.[32 33] First, for all patients diagnosed between 1996 and 2005 we estimated the probability that each patient would receive a PET scan, as a function of all patient characteristics

used in Models 1-3 (except for stage or survival for analyses of stage and survival, respectively), cancer registry, and interaction of each variable with year. We then used this estimated probability as a propensity score to indicate the likelihood that a patient would receive a PET scan based on available patient characteristics. Nearest available matching by propensity score was used to match patients receiving vs. not receiving PET.[32 33] Propensity matched patients who actually did and did not receive a PET scan were then analyzed using multivariable regression analysis. The quality of the propensity score match was evaluated by univariate analysis of patient characteristics and plotting propensity score distributions before and after matching.

Additional sensitivity analyses were also conducted. Regression analyses were repeated controlling for SEER registry to ensure findings were not registry specific. Sensitivity to changes in the collection and/or reporting of SEER NSCLC stage in 1998 and again in 2004 was evaluated by repeating the analysis limited to patients diagnosed between 1998 and 2003. All survival analyses were repeated using a minimum survival of 4 months to assess sensitivity to the 2-month survival inclusion criteria. Errors were clustered by SEER registry for all regressions[34]. Significance was assessed using a cutoff of $P < 0.001$ to control false positives from multiple hypothesis testing. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary NC).

6.3 Results

Study Population

We identified 204,664 Medicare beneficiaries diagnosed with cancer of the lung and bronchus in the included SEER registries between 1993 and 2005. From these beneficiaries we identified 207,291 cases of incident lung cancer. We sequentially excluded patients (**Figure 6.2**) who were diagnosed at death or autopsy, were younger than 66 years of age, did not have microscopically-confirmed NSCLC histology, had another malignancy in the year before or after their diagnosis, participated in an HMO or did not have part A and B coverage for the year before and after their diagnosis, did not survive a minimum of 2 months from their diagnosis, did not have an undocumented prior malignancy. Patients were additionally required to have a Medicare claims-based ICD-9 diagnosis of lung cancer within two months prior to and four months following SEER diagnosis. The final cohort consisted of 58,575 NSCLC cases.

To analyze the effect of PET over time, we designated three periods for longitudinal comparison of PET vs. non-PET NSCLC diagnoses: pre- (1993-1994), initial (1998-1999), and post- (2004-2005) PET periods. Patients diagnosed during different cohorts exhibited significantly different patient demographics (**Table 6.1)**. In later years, NSCLC Medicare patients were composed of a larger percentage of patients older than 80 years old, female patients, blacks, patients with comorbidities, and non-married patients ($P<0.0001$). Patients who received PET were demographically distinct from patients who did not receive a PET scan and were more likely to be black, not receive treatment, and to come from sociodemographically disadvantaged census tracks (**Table 6.2**).

Increased Use of PET and Stage Migration

As reported previously[31], the use of PET spread rapidly from 1998 to 2005, with an increase from 5% to 60% of NSCLC patients receiving one or more PET scans in the initial vs.

post-PET patient cohorts (P<0.0001; **Table 6.3**). Increased rates of PET use between 1998 and 2005 were accompanied by an increase in the proportion of patients with advanced disease (stage IIIB and IV; **Figure 6.3**), whereas the incidence of unstaged disease decreased in later cohorts (P<0.0001). Stage IV disease experienced the largest absolute increase, increasing from 23% 33% between 1993 and 2005. Prior to 1998, the proportion of patients with advanced disease remained stable at 40%. The increase in the proportion of patients with advanced stage disease following the introduction of PET persisted after stratifying by demographic subgroups based on race, region, age, and number of comorbidities (**Figure 6.4**). The incidence of unstaged disease declined from 26% in 1993 to 10% by 2005. Patients with unstaged disease were less likely to undergo treatment of any kind or to receive a PET scan and were more likely to be older, have more comorbidities, and were the only patients with carcinoid tumors (P<0.0001).

In addition to clinical AJCC staging, we observed an increase in the frequency of advanced stage disease among the overall Medicare NSCLC population across all staging systems available through the SEER registry including the modified AJCC, SEER summary, and SEER historical staging systems (**Figure 6.3**). Patients that were unstaged using strict AJCC 3rd edition criteria were predominantly (60%) reclassified as early disease by the SEER-modified AJCC stage.

Because the information used to obtain SEER AJCC stage changed in 1998 and again in 2004 we alternatively examined changes in stage distribution between patients diagnosed in 1998-1999 vs. 2002-2003. We observed similar changes over this time period. Stage IV disease increased by 5.7% from 43.6% to 49.2% (P<0.0001), unstaged disease decreased by 5.5% from 20.7% to 15.2%, and PET utilization increased from 4.7% to 44.7% from 1998-1999 to 2002-2003.

Selective Administration of PET to Patients with Early Stage Disease

PET was selectively administered to patients with early stage disease by both univariate and multivariable regression analyses. In univariate analyses, patients who received PET had lower rates of advanced stage disease. Patients receiving PET had an increased incidence of stage I disease (31% vs. 20%) and decreased incidence of stage IV disease (24% vs. 31%; **Table 6.4**). Among patients within the 2004-2005 cohort, 70% of those with early or unknown stage disease received a PET scan compared with 50% of patients with advanced stage disease. We found similar results using multivariable analyses that controlled for patient demographics, which revealed that the administration of PET predicted a 50% decreased likelihood of being diagnosed with stage IV disease (**Table 6.5**). Regression models restricted to patients propensity score matched by survival and demographic characteristics (N=14,444) yielded similar findings.

Survival Analyses

Following the introduction of PET in 1998, stage-specific survival improved or remained the same across all stages (**Figure 6.4**). During this same period, overall survival remained relatively constant. Specifically, a non-significant trend towards an increase in overall survival of less than 2% occurred between the initial and post-PET adoption periods (1998-1999 vs. 2004-2005; Table 3; $P = 0.01$). Sensitivity analysis examining changes between 1998-1999 and 2002-2003 revealed no change in overall 2-year survival (33.7% vs. 33.6%; P = 0.85). Larger improvements in two-year survival rates occurred in the overall population in the period extending prior to PET between 1993 and 2005 (3.7%; **Table 6.3**) and were concentrated among older patients and patients with multiple comorbidities (**Figure 6.5**). Following the introduction

of PET, stage-specific survival remained unchanged or improved, with a large increase in survival among patients with advanced stage disease. Two-year survival for advanced stage disease was stable at 10% in the years prior to 1998 and had increased to 16% by 2005. In univariate analysis, survival was significantly higher among patients who received PET vs. patients who did not receive PET (46% vs. 29%, P<0.001; **Table 6.4**).

Multivariable regression analysis was used to assess the association of PET with patient overall survival at two years, controlling for patient demographics and year of diagnosis (**Table 6.5**). Models were analyzed both excluding (model 2) and including (model 3) NSCLC stage to examine the effect of stage migration on the association between PET and survival. In both models the receipt of PET was significantly (P<0.0001) associated with improved patient survival. Controlling for stage resulted in a much smaller survival advantage being associated with PET, reducing the survival odds ratio of PET from 2.6 to 1.4, suggesting a significant contribution of stage migration to the observed benefit of PET. Both models found decreased survival associated with being older, having comorbidities, living in areas with lower education, being male, and being not married. Increasing stage was associated with progressively worse two-year survival (model 3, P<0.0001). Regression models restricted to patients propensity score matched by stage and demographics (N=2,924) yielded similar findings.

Propensity Matched Sensitivity Analysis

Patients were separately matched in order to allow comparison of either stage or survival. Analysis of stage was performed on patients matched for survival, while analysis of survival was matched for stage. A total of 38,359 cases diagnosed between 1996 and 2005 had all covariates

available for matching. A total of 14,444 patients who did and did not receive a PET scan were matched for their propensity to receive a PET scan for stage analysis. A total of 2,924 patients were similarly matched for survival analysis. Distribution of patient PET propensity scores were similar among matched, but not unmatched, patients who had vs. had not received a PET scan (**Figure 6.5**). Unmatched patients who received PET were demographically distinct from patients who did not receive a PET scan and were more likely to be black, not receive treatment, and to come from sociodemographically disadvantaged census tracks (**Table 6.2**). Patients with matched propensity to receive PET were demographically similar between patients who did and not receive a PET scan (**Table 6.6**).

Sensitivity Analyses

Matching by propensity score, limiting analysis to patients diagnosed between 1998 and 2003, controlling for SEER registry, limiting analysis to patients surviving 4 months or more, and limiting survival analysis to early stage disease did not qualitatively change any reported trends or results unless specifically stated above.

6.4 Discussion

In this study, we provide evidence that the widespread adoption of PET within the Medicare NSCLC population between 1998 and 2005 was not accompanied by improved patient survival. Instead, we found that the adoption of PET was characterized by stage migration, improvement in stage-specific survival, and selective administration of PET to patients with early stage disease. Our findings here suggest that previous epidemiologic associations between

PET and improved patient outcomes may be a manifestation of PET-induced stage migration and selective administration of PET to patients with early stage disease.

Following the introduction of PET in 1998 we observed significant stage migration within the Medicare NSCLC population, which was characterized by an increase in advanced stage disease. Between 1997 and 2003, the proportion of all Medicare NSCLC patients with advanced or stage IIIB/ IV disease increased by 10%, coinciding with an increase in PET utilization from 0% to 50%. We observed an increase in advanced or distant disease using both clinically (clinical and modified AJCC 3rd edition) and longitudinally relevant (SEER summary and SEER historic) staging systems. This increase in advanced stage disease was observed both overall analyses and after stratification by demographic subgroups, suggesting that the observed stage migration was not due to demographic shifts over time in patient age, race, number of comorbidities, or region. Superimposed on the increase in stage IV disease was a steady decline in unstaged disease from 1993 through 2005. It is possible that the use of PET may have reduced the number of patients with unstaged disease, however it is important to note that a decrease in patients with unstaged disease was also observed prior to the introduction of PET.

We found that PET was selectively administered to patients with early stage disease by both univariate and multivariable regression analyses. Patients who received PET had a roughly 50% higher proportion of early disease and 50% lower proportion of stage IV disease compared to patients who did not receive a PET scan, with PET being used in 70% of early stage disease vs. 50% of advanced stage disease patients by 2004-2005. We found similar results using multivariable analyses that controlled for patient demographics, which revealed that the administration of PET was half as likely in patients with stage IV disease. PET is a more sensitive modality for detecting extent of disease, which is generally used after conventional

diagnostic and imaging workup has been completed. Because PET is used in addition to existing staging modalities, the use of PET should only be able to increase the stage of newly diagnosed disease. As a result, we predicted that the use of PET would be positively associated with increased disease stage. Instead, we found that PET was negatively associated with advanced stage disease. Because PET cannot be used to downstage disease, the only plausible explanation for this is that PET was preferentially administered to patients with early stage disease. This is likely due to the appropriate use of PET in evaluating primarily localized disease for evidence of occult metastases and avoidance of PET use in frank metastatic disease in line with 2003 recommendations by the American Society of Clinical Oncologists (ASCO). [4] PET may be less likely to be used in patients with poor performance status or in patients with improved health care access, which we were unable to measure in our study. Limiting the analysis to patients who survived 4 months from observation did not affect analysis results, suggesting that poor performance status was not the dominant factor driving selective administration of PET to patients with non-metastatic disease.

We found that the combination of PET-induced stage migration and selective administration of PET to patients with early stage disease resulted in an association of PET with improved survival. Following the introduction of PET in 1998, stage-specific survival improved or remained the same across all stages. The largest increase was observed among advanced stage disease, which experienced an increase in 2 year survival from 10% to 15%. During this period, overall survival remained relatively constant. Specifically, no significant change in overall survival occurred between the initial and post-PET adoption periods (1998-1999 vs. 2004-2005). Stable or increased stage-specific survival across all stages in the absence of overall increases in survival can only be mathematically explained by migration of patients between stage groups,

indicating that stage-specific increases in survival were predominantly an artifact of stage migration. Interpretation of multivariable regression analyses was complicated by the presence of selection bias and stage migration. Regression models that controlled for stage attributed a much smaller survival advantage to PET, reducing the odds ratio associated with PET from 2.6 to 1.4, suggesting a significant contribution of stage migration to the observed benefit of PET.

PET and stage are both causally related to one another, endogenous, and therefore subject to bias when modeled with conventional survival analysis techniques. Combined with the presence of significant stage migration, this endogeneity may explain previous associations between the use of PET and improved patient survival. A previous analysis in a privately insured population by Chee et al. [12] similarly found a direct association between the use of PET and roughly two-fold improved survival in the absence of any change in overall patient survival. Previous work by Farjah et al. [3] suggested that PET was similarly associated with a two fold increase in survival, but did not control for selection bias or stage migration. Had a two-fold gain in survival been truly afforded by the use of PET, overall improvement in NSCLC survival should have increased by over 25% following uptake of PET by more than half of the Medicare NSCLC population. This finding was not observed in our study and has not been previously reported in the literature, therefore it is unlikely that PET use itself was responsible for improvements in stage-specific survival but rather the Will-Rogers effect of reallocation of patients to different stage categories based upon the application of PET.[12] Stage-specific increases in survival of advanced stage NSCLC [28] are also consistent with this observation. Taken together, our findings urge caution for future work seeking to establish a causal relationship between imaging and outcomes.

To date, there have been only four RCTs examining the use of PET in NSCLC, which have consistently demonstrated PET-induced upstaging of disease but have not detected a change in patient survival in the setting of limited statistical power. [7-10] In addition to their being a lack of empirical evidence supporting a survival advantage of PET, it is not clear how PET would increase survival of advanced stage disease for which there is no cure. In the case of stage IV disease, we observed an increased in survival from 10% to 15%, or a relative 50% increase in survival. Others have previously observed improved survival in advanced NSCLC disease and have concluded that these improvements have been a result of improved treatment. [35] Stage migration would explain both this large improvement in incurable disease and the simultaneous lack of change in survival in the overall NSCLC population, a phenomena previously dubbed the Will Rogers phenomena[12,30].

Over the extended 1993-2005 period, we observed an increase in overall survival of 3.7 percentage points, which occurred largely prior to the introduction of PET in 1998. This could reflect improved management of cancer, including antineoplastic therapies and supportive care (i.e. growth factors), management of patient comorbidities, or perhaps earlier detection coinciding with increased use of CT, MRI, or other imaging modalities. Since 1997, ASCO guidelines have recommended a combination of radiation and chemotherapy for patients with good performance status and unresectable (typically stage III or IV) disease. [4] In 2003, the ASCO recommendation was further expanded to recommend the use of dual vs. single chemotherapy agents. Recently, a randomized trial of early palliative care found a survival benefit comparable to chemotherapy, [36] highlighting the potential for other factors besides chemotherapy to have affected patient survival. The effect of increasing chemotherapy use on overall survival may have affected the trends in survival that we observed in our study. A

modest increase in the survival of patients older than 80 and patients with multiple comorbidities lends support to idea of modestly improved supportive care of older or moribund patients during the study period.

PET has the potential to provide value to patients, physicians, and potentially health care insurers regardless of whether or not PET is capable of improving patient outcomes. The use of PET, particularly in conjunction with dedicated dual PET/CT scanners, provides more sensitive and specific staging of NSCLC compared with CT alone[4-6] and may facilitate physician-patient communication regarding patient prognosis and treatment options. The ability of PET to impact survival may change in the future with the use of PET in evaluating emerging molecularly-targeted therapies, which were infrequently used during the time frame analyzed by this study. Another potential benefit of PET is the avoidance of futile thoracotomy, which occurs when a patient with occult metastatic disease undergoes local, definitive treatment for an incurable disease. Of the four randomized trials investigating the use of PET in NSCLC to date, three have suggested that the use of PET may result in appropriate upstaging and reduction of futile thoracotomy[7-9] and one has suggested potential cost savings,[37] although it is unknown whether or not these benefits can be extrapolated from small, single center RCTs to the general Medicare NSCLC population. Continuing evaluation of the effect of PET on cancer patient evaluation, management, and outcomes will likely be aided in the future by the continued implementation of national, prospective databases of PET use such the National Oncologic PET Registry (NOPR).[38-40]

There are a number of topics regarding the use of PET in cancer patients that may warrant further research. The ability of PET to impact survival may change with the emergence of molecularly-targeted therapies, which were infrequently used during the time frame analyzed

by this study. The increased use of PET and its role in clinical decision making and use, timing, and value in conjunction with other diagnostic and evaluative tests are also areas of future research. How patient performance status affects the likelihood of receiving PET might help provide a more accurate model of how performance status affects imaging use and how these factors might impact attempts to legislate changes in health care reform. Our findings urge caution for future studies that seek to establish a causal relationship between imaging and outcomes. Future research to improve or create new methodologies capable of accurately addressing such questions in the setting of endogeneity would be extremely valuable. Of note, a decrease in patients with unstaged disease was also observed prior to the introduction of PET. How and why this change occurred might help further inform studies involved NSCLC staging in ongoing research.

Limitations

This study was a retrospective, claims-based analysis. Only PET scans paid for by Medicare could be detected in our analysis. However, it is likely that relatively few PET scans for Medicare beneficiaries would be paid by third party insurers or out of pocket. To minimize the proportion of missed claims, all analyses were limited to Medicare beneficiaries with both part A and B coverage and no HMO participation or part C coverage for the 12 months prior to and following their diagnosis. Patients within the SEER registry are overall more likely to be non-white, live in non-poverty areas, and live in urban areas,[34] and may as a result reflect a skewed characterization of PET within the general Medicare NSCLC population. The most recent year of diagnosis examined in this study was 2005, which is the most recent SEER cohort available for which two full years of survival follow-up were available to determine 2-year

survival. Lastly, collection of cancer T, N, and M information used to extract cancer stage changed in 1998 and again in 2004.[25] Prior to 1998, information used to stage cancers was obtained using all available information in the two months following diagnosis. Beginning in 1998 onward, this timeframe was extended to four months or first surgery. This likely resulted in a slight increase in advanced stage disease between 1997 and 1998. In 2004, data collection within SEER changed from the extend of disease (EOD) collection system to the collaborative staging system (CSS). It is unclear how this should have affected staging. Of note, we did observe a slight decrease in advanced stage disease and increase in early stage disease between 2003 and 2004, which we attribute to this change. Regardless, no changes in the staging system were made between 1998 and 2003, when we observed the largest changes in PET utilization and stage migration.

Conclusions

In this study we show that overall two-year survival of NSCLC Medicare patients has remained relatively constant following the widespread adoption of PET. Previous reports demonstrating an association of PET with large increases with NSCLC patient survival during this period are likely explained by a combination of stage migration and preferential administration of PET to patients with less advanced disease. Emerging screening technologies and treatments must be rigorously evaluated to prevent physicians, policy makers, insurers, and patients from making misinformed decisions about their health care as a result of unappreciated selection bias and/or stage migration. The ability of PET to affect patient management, health care utilization, and costs remain important areas of ongoing research that may change as new treatments become available in the future.

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Table 6.1 –Baseline Patient Characteristics by Pre-PET (1993-1994), Initial PET (1998-1999), and Post-PET Cohorts (2004-2005)

Characteristic	Year of Diagnosis			*P*-Value*
	Pre-PET (1993-1994) N = 8,837	Initial PET (1998-1999) N = 8,017	Post-PET (2004-2005) N = 10,436	
Age > 80, No. (%)	1287 (14.6)	1460 (18.2)	2342 (22.4)	<0.0001
Male, No. (%)	5111 (57.8)	4416 (55.1)	5312 (50.9)	<0.0001
Black, No. (%)	672 (7.6)	670 (8.4)	862 (8.3)	<0.0001
Comorbid conditions, No. (%)				<0.0001
0	5404 (61.2)	4514 (56.3)	5186 (49.7)	
1	2283 (25.8)	2185 (27.3)	3071 (29.4)	
2+	1150 (13)	1318 (16.4)	2179 (20.9)	
Census tract characteristics (2000): (Highest Quartile)				
Did not complete high school	---	1687 (25.8)	2135 (23)	c
Percent below poverty line	---	1704 (26.1)	2156 (23.3)	<0.0001
Percent black	---	1608 (24.6)	2211 (23.8)	0.25
Married (%)	5024 (56.9)	4533 (56.5)	5496 (52.7)	<0.0001
Metropolitan (%)	7748 (87.7)	6819 (85.1)	8977 (86)	<0.0001
Any Therapy (%)	7626 (86.3)	6791 (84.7)	8755 (83.9)	<0.0001
Region				<0.0001
West	3894 (44.1)	3464 (43.2)	4749 (45.5)	
Midwest	2920 (33)	2847 (35.5)	3376 (32.4)	
Northeast	1417 (16)	1156 (14.4)	1626 (15.6)	
South	606 (6.9)	550 (6.9)	685 (6.6)	

* Chi-squared test. Abbreviations: HS, High School

Table 6.2 – Baseline Patient Characteristics by Receipt of PET, 1996-2005

Characteristic	Receipt of PET		*P*-Value*
	No PET (N=27,196)	PET (N=11,163)	
Age > 80, No. (%)	5278 (19.4)	1956 (17.5)	<0.0001
Male, No. (%)	14612 (53.7)	5730 (51.3)	<0.0001
Black, No. (%)	2434 (9)	662 (5.9)	<0.0001
Comorbidities, No. (%)			<0.0001
0	14917 (54.9)	5758 (51.6)	
1	7505 (27.6)	3263 (29.2)	
2+	4774 (17.6)	2142 (19.2)	
Census tract characteristics (2000): (Highest Quartile)			
Did not complete HS	7248 (26.7)	2218 (19.9)	<0.0001
% below poverty line	7183 (26.4)	2212 (19.8)	<0.0001
Percent black	7026 (25.8)	2362 (21.2)	<0.0001
Married (%)	14609 (53.7)	6223 (55.8)	<0.0001
Metropolitan (%)	23070 (84.8)	9707 (87)	<0.0001
Any Therapy (%)	22455 (82.6)	10059 (90.1)	<0.0001
Region			<0.0001
West	11986 (44.1)	5276 (47.3)	
Midwest	9708 (35.7)	3232 (29)	
Northeast	3554 (13.1)	2000 (17.9)	
South	1948 (7.2)	655 (5.9)	

* Chi-squared test. Abbreviations: HS, High School

Table 6.3 –PET utilization, Survival, and Stage by Pre-PET (1993-1994), Initial PET (1998-1999), and Post-PET Cohorts (2004-2005)

Characteristic	Year of Diagnosis			*P*-Value*
	Pre-PET (1993-1994) N = 8,837	Initial PET (1998-1999) N = 8,017	Post-PET (2004-2005) N = 10,436	
Any PET scans, No. (%)	0 (0)	380 (4.7)	6303 (60.4)	<0.0001
Any PET Facility, No. (%)	0 (0)	954 (11.9)	7476 (71.6)	<0.0001
Any PET Physician, No. (%)	0 (0)	1263 (15.8)	10238 (98.1)	<0.0001
Miles to PET ≤ 40, No. (%)	0 (0)	4942 (61.6)	9708 (93)	<0.0001
Alive at 2 years, No. (%)	2809 (31.8)	2703 (33.7)	3709 (35.5)	<0.0001†
Stage (AJCC 3rd Edition)				<0.0001
I	1933 (21.9)	1848 (23.1)	2651 (25.4)	
II	385 (4.4)	260 (3.2)	438 (4.2)	
IIIA	742 (8.4)	757 (9.4)	1244 (11.9)	
IIIB	1466 (16.6)	1462 (18.2)	1655 (15.9)	
IV	2017 (22.8)	2030 (25.3)	3404 (32.6)	
Unstaged	2294 (26.0)	1660 (20.7)	1044 (10.0)	

* Chi squared test was used to test for an association between categorical variables and year of diagnosis.
† P-Value for the difference between initial-PET and post-PET survival is not significant (P = 0.01)
Abbreviations; PET, Positron Emission Tomography; AJCC, American Joint Committee on Cancer

Table 6.4: PET utilization, Survival, and Stage by Receipt of PET, 1996-2005

Characteristic	Receipt of PET		*P*-Value*
	No PET (N=27,196)	PET (N=11,163)	
Any PET scans, No. (%)	0 (0)	11163 (100)	<0.0001
Any PET Facility, No. (%)	6420 (23.6)	8796 (78.8)	<0.0001
Any PET Physician, No. (%)	11025 (40.5)	11154 (99.9)	<0.0001
Miles to PET ≤ 40, No. (%)	15970 (58.7)	10258 (91.9)	<0.0001
Alive at 2 years, No. (%)	7906 (29.1)	5078 (45.5)	<0.0001
Stage (AJCC 3rd Edition)			<0.0001
I	5478 (20.1)	3400 (30.5)	
II	828 (3)	543 (4.9)	
IIIA	2400 (8.8)	1491 (13.4)	
IIIB	5073 (18.7)	1796 (16.1)	
IV	8447 (31.1)	2651 (23.8)	
Unstaged	4965 (18.3)	1282 (11.5)	

* Chi-squared test. Abbreviations: HS, High School; PET, Positron Emission Tomography; AJCC, American Joint Committee on Cancer

Table 6.5: Multivariable Logistic Regression of the Likelihood of Stage IV disease and 2-Year Survival as a Function of PET (N = 38,359).

Characteristic	Model 1	Model 2	Model 3
	Stage IV disease as a function of PET OR (95% CI)	2-Yr Survival as a function of PET OR (95% CI)	2-Yr Survival as a function of PET, controlling for stage OR (95% CI)
Any PET	0.44 (0.39-0.49)*	2.58 (2.37-2.82)*	1.4 (1.28-1.53)*
Any PET Facility	1.13 (1.05-1.22)	1.01 (0.94-1.07)	1.08 (1-1.16)
Any PET Physician	1.18 (1.06-1.32)	0.87 (0.75-1.01)	0.91 (0.81-1.03)
PET > 40 miles away	0.95 (0.88-1.02)	0.98 (0.92-1.04)	0.98 (0.91-1.05)
Year of Diagnosis			
1996	0.88 (0.82-0.95)	0.97 (0.9-1.05)	0.89 (0.8-0.98)
1997	0.88 (0.77-0.99)	1.02 (0.9-1.15)	0.94 (0.84-1.05)
1998 (Reference)	---	---	---
1999	1.01 (0.89-1.14)	1.05 (0.94-1.17)	1.05 (0.95-1.16)
2000	0.99 (0.86-1.14)	1.07 (0.91-1.26)	1.07 (0.91-1.24)
2001	1.18 (0.97-1.44)	0.85 (0.75-0.96)	0.92 (0.83-1.01)
2002	1.33 (1.13-1.56)*	0.76 (0.66-0.88)*	0.83 (0.74-0.94)
2003	1.48 (1.31-1.68)*	0.73 (0.62-0.86)*	0.87 (0.75-1.01)
2004	1.66 (1.42-1.95)*	0.74 (0.62-0.89)	0.87 (0.74-1.02)
2005	1.88 (1.6-2.22)*	0.7 (0.6-0.82)*	0.82 (0.72-0.93)
Stage (AJCC 3rd Ed)			
II	---	---	0.52 (0.47-0.58)*
IIIA	---	---	0.19 (0.17-0.21)*
IIIB	---	---	0.08 (0.08-0.09)*
IV	---	---	0.04 (0.03-0.04)*
Unstaged	---	---	0.21 (0.19-0.23)*
II x PET	---	---	1.08 (0.96-1.22)
IIIA x PET	---	---	1.26 (1.07-1.48)
IIIB x PET	---	---	1.9 (1.62-2.23)*
IV x PET	---	---	2.1 (1.7-2.61)*
Unstaged x PET	---	---	1.32 (1.11-1.57)
Age >80	0.78 (0.72-0.83)*	0.64 (0.62-0.66)*	0.58 (0.55-0.61)*
Black	1.14 (1.01-1.28)	0.85 (0.8-0.91)*	0.97 (0.9-1.03)
Comorbidities			
One	0.76 (0.72-0.8)*	0.98 (0.92-1.04)	0.82 (0.75-0.9)*
Multiple	0.68 (0.66-0.71)*	0.79 (0.73-0.85)*	0.61 (0.56-0.66)*
Male	1.07 (0.93-1.23)	0.57 (0.55-0.61)*	0.57 (0.54-0.59)*
Married (%)	0.99 (0.9-1.09)	1.26 (1.17-1.35)*	1.29 (1.18-1.41)*
Metropolitan (%)	0.98 (0.89-1.08)	1.09 (0.93-1.27)	1.1 (0.91-1.32)
Region			
Midwest	0.89 (0.82-0.96)	1.04 (0.96-1.14)	0.96 (0.9-1.03)
Northeast	0.95 (0.88-1.03)	1.08 (1.03-1.14)	1.04 (0.99-1.09)
South	0.87 (0.76-1)	0.83 (0.75-0.93)*	0.77 (0.69-0.84)*

*P < 0.001, Census tract variables were omitted due to space constraints.

Abbreviations: PET, Positron Emission Tomography; AJCC, American Joint Committee on Cancer

Table 6.6: Univariate Comparison of Patients by Receipt of PET Before and After Matching by PET Propensity for Stage and Survival Analysis, 1996-2005.

Characteristic	Propensity Matched for Stage Analysis (Matched for Survival)		Propensity Matched for Survival Analysis (Matched for Stage)	
	No PET (N=7,222)	PET (N=7,222)	No PET (N=1,462)	PET (N=1,462)
Any PET scans, No. (%)	0 (0)*	7222 (100)*	0 (0)*	1462 (100)*
Alive at 2 years, No. (%)	2257 (31.3)	2304 (31.9)	---	---
Stage (AJCC 3rd Edition)				
I	---	---	1462 (100)	1462 (100)
II	---	---	<11 (<1.0)	<11 (<1.0)
IIIA	---	---	<11 (<1.0)	<11 (<1.0)
IIIB	---	---	<11 (<1.0)	<11 (<1.0)
IV	---	---	<11 (<1.0)	<11 (<1.0)
Unstaged	---	---	<11 (<1.0)	<11 (<1.0)
Any PET Physician, No. (%)	7211 (99.8)	7213 (99.9)	1462 (100.0)	1462 (100.0)
Miles to PET ≤ 40, No. (%)	6569 (91.0)	6566 (90.9)	1317 (90.1)	1317 (90.1)
Age > 80, No. (%)	1413 (19.6)	1399 (19.4)	284 (19.4)	290 (19.8)
Male, No. (%)	3745 (51.9)	3792 (52.5)	722 (49.4)	735 (50.3)
Black, No. (%)	6692 (92.7)	6710 (92.9)	100 (6.8)	91 (6.2)
Comorbidities, No. (%)				
0	3772 (52.2)	3792 (52.5)	682 (46.6)	707 (48.4)
1	2051 (28.4)	2037 (28.2)	456 (31.2)	459 (31.4)
2+	1399 (19.4)	1393 (19.3)	324 (22.2)	296 (20.2)
Census tract characteristics (2000): (Highest Quartile)				
Did not complete HS	1630 (22.6)	1596 (22.1)	332 (22.7)	338 (23.1)
% below poverty line	1604 (22.2)	1583 (21.9)	327 (22.4)	341 (23.3)
Percent black	1655 (22.9)	1635 (22.6)	339 (23.2)	341 (23.3)
Married (%)	3892 (53.9)	3925 (54.3)	810 (55.4)	795 (54.4)
Metropolitan (%)	6246 (86.5)	6259 (86.7)	1280 (87.6)	1279 (87.5)
Any Therapy (%)	5975 (82.7)	6420 (88.9)	1348 (92.2)	1389 (95.0)
Region				
West	3285 (45.5)	3284 (45.5)	640 (43.8)	658 (45.0)
Midwest	2429 (33.6)	2408 (33.3)	527 (36.0)	517 (35.4)
Northeast	1082 (15.0)	1097 (15.2)	204 (14.0)	212 (14.5)
South	426 (5.9)	433 (6.0)	91 (6.2)	75 (5.1)

* $P < 0.001$, Chi-squared test. Abbreviations: HS, High School

Figure 6.1: Conceptual Schematic of Stage Migration as a Result of PET.

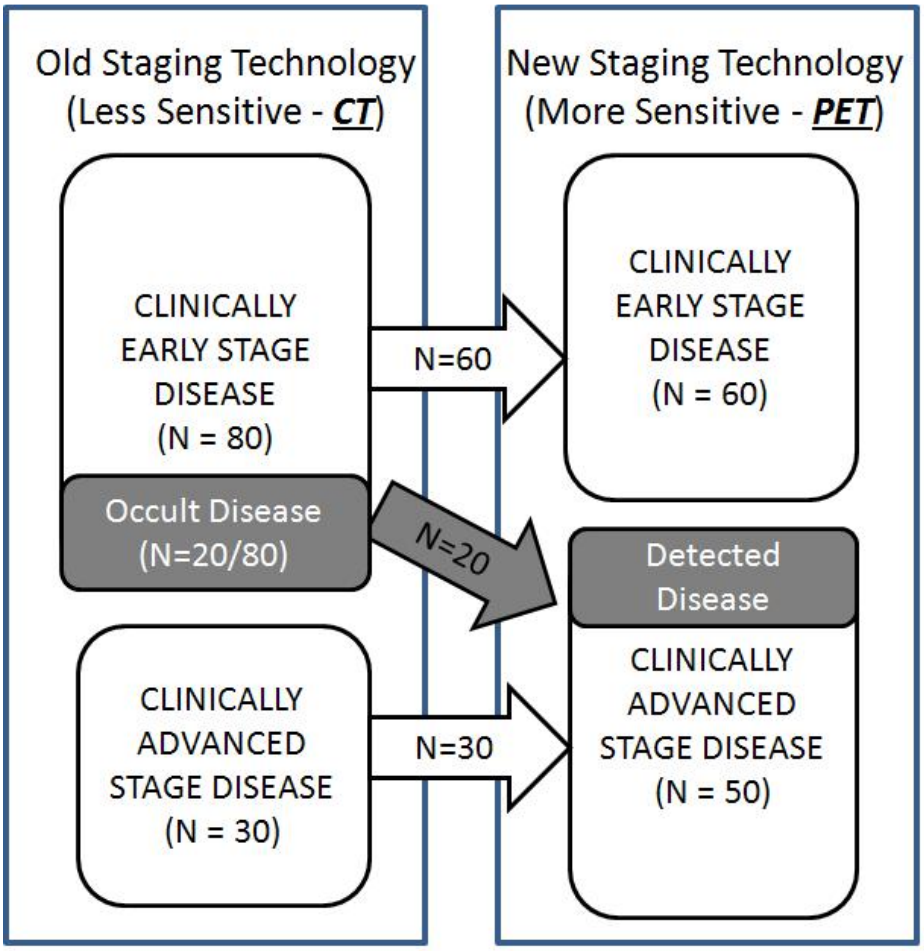


Figure 6.2: CONSORT diagram

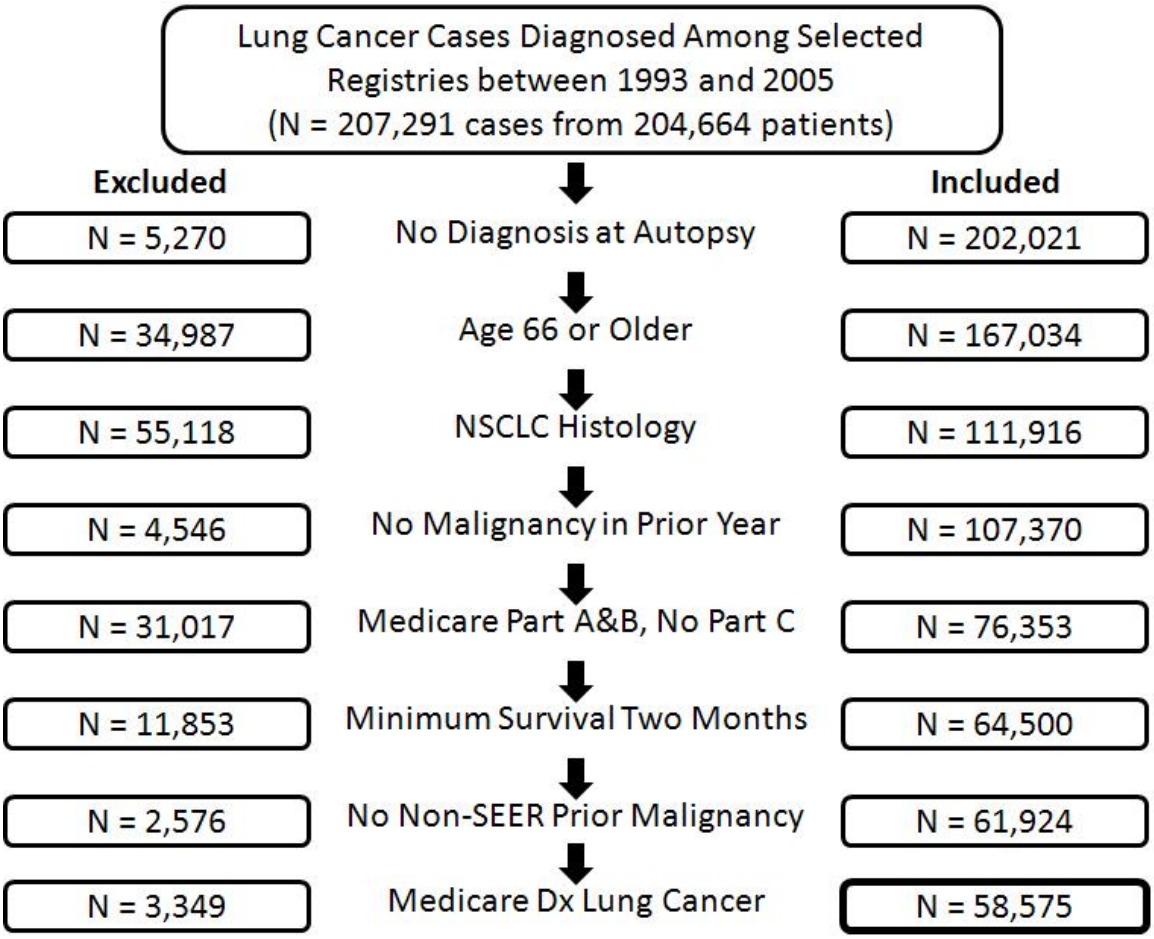


Figure 6.3: Stage Distribution by Alternative Staging Systems among NSCLC Medicare Patients from 1993 to 2005.

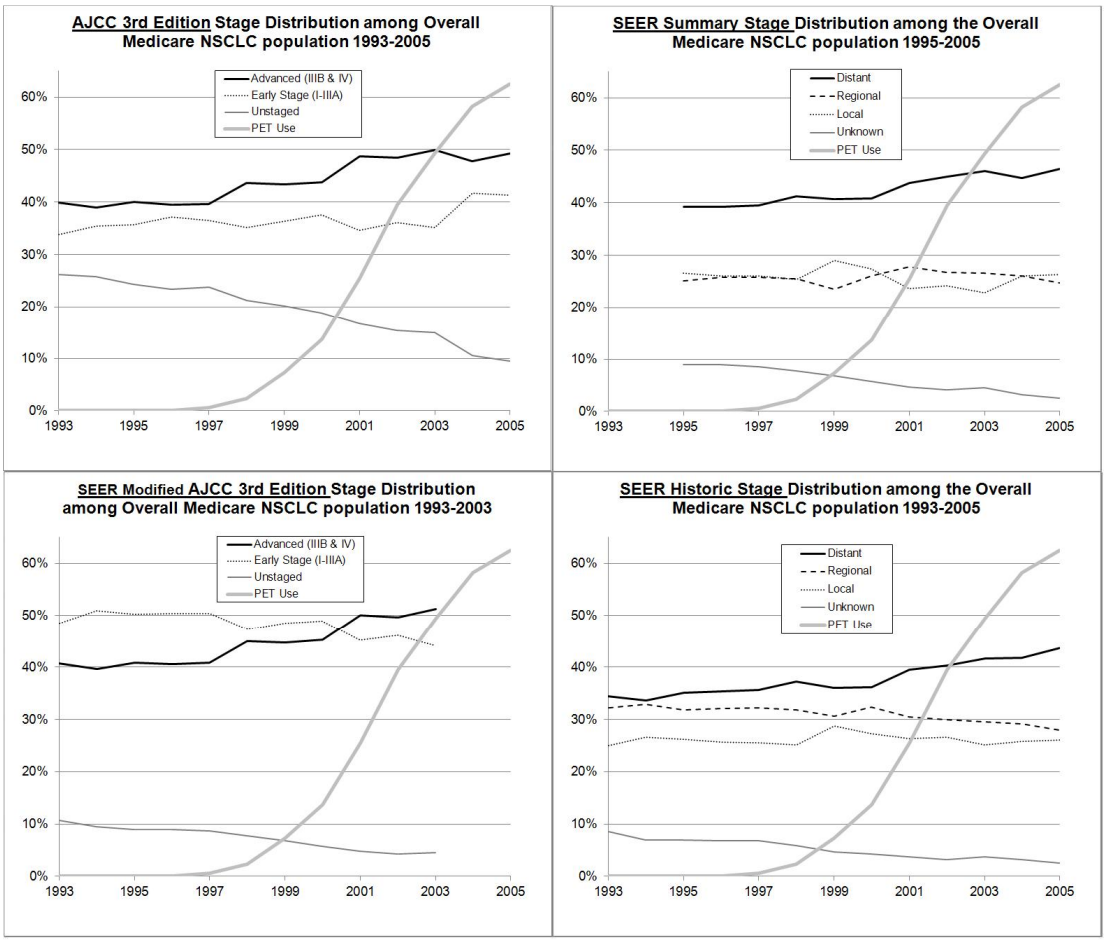


Figure 6.4: Stage Distribution and 2-Year Survival by Selected NSCLC Medicare Patient Subgroups from 1993 to 2005.

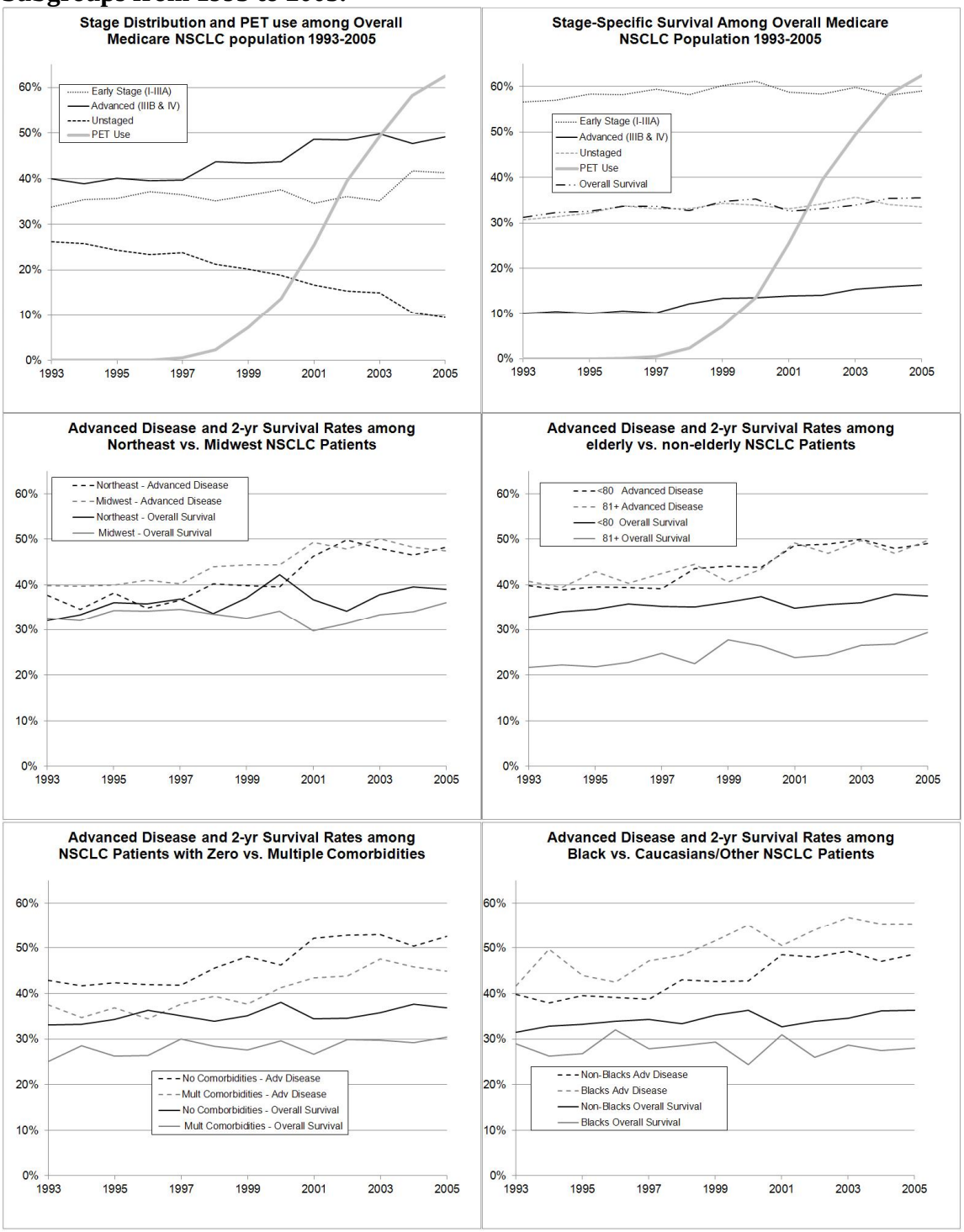
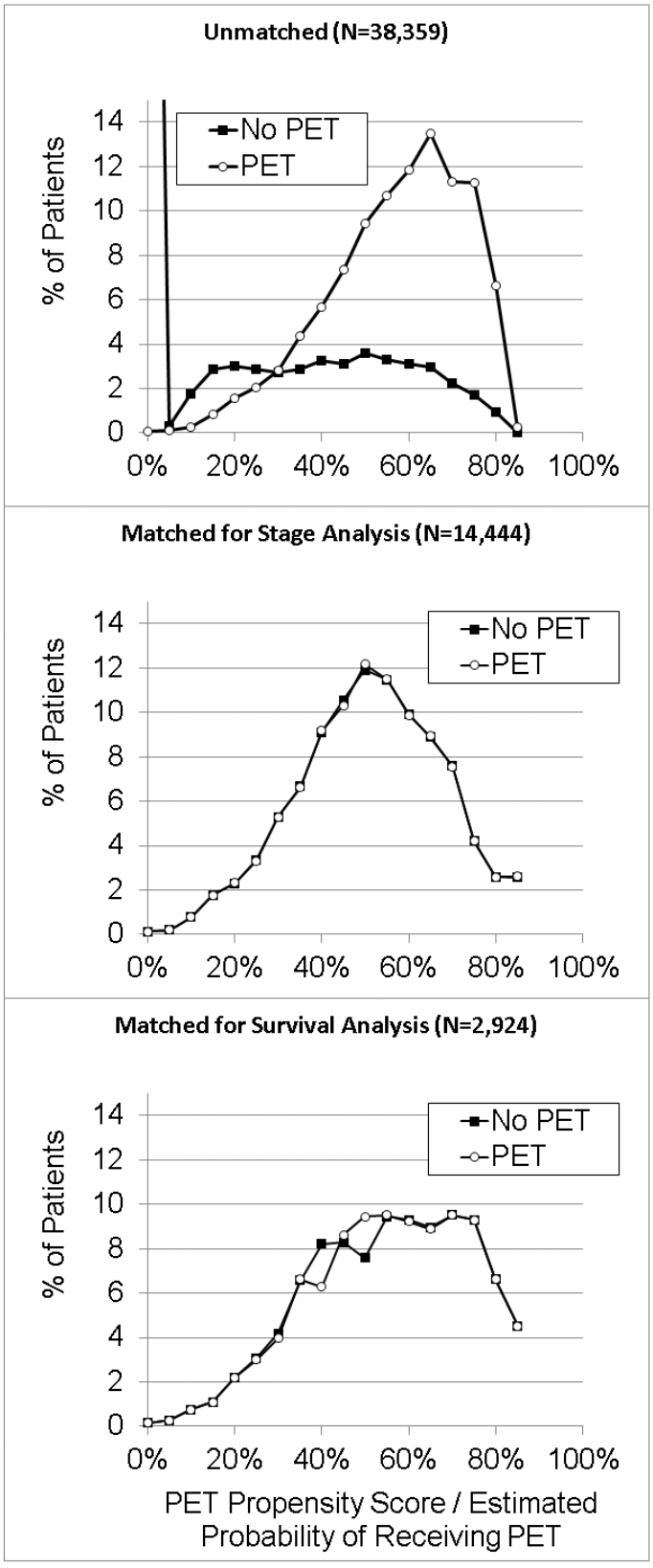


Figure 6.5: Distribution of PET Propensity Before and After Matching, 1996-2005.



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CHAPTER 7: THE ASSOCIATION OF PET WITH TRENDS IN THE TREATMENT AND HEALTH CARE UTILIZATION OF THE MEDICARE NON-SMALL CELL LUNG CANCER POPULATION BETWEEEN 1998 AND 2005

Abstract

Context:

The use of positron emission tomography (PET) spread rapidly among Medicare non-small cell lung cancer (NSCLC) beneficiaries following its approval in 1998. Small randomized trials suggest that PET has the potential to save costs by reducing rates of futile thoracotomy. The use of PET in such trials, however, may differ systematically from how this technology has been used in clinical practice within the Medicare NSCLC population. How PET affects treatment decisions and overall health care costs of NSCLC patients is an important question that has not been studied previously within the Medicare NSCLC patient population.

Objective:

To examine the association of PET with changes in treatment and overall healthcare costs among Medicare NSCLC beneficiaries.

Design, Setting, and Patients:

Using Surveillance Epidemiology and End Results (SEER)-Medicare data, we conducted a retrospective cohort study of NSCLC Medicare beneficiaries diagnosed with NSCLC between 1993 and 2005.

Main Outcome Measures:

Receipt of surgical resection, inpatient costs, and overall health care costs.

Results:

A total of 58,575 cases of Medicare NSCLC met study criteria between 1993 and 2005. From 1998 to 2005, the proportion of NSCLC cases receiving a PET scan increased from 5% to 60%. During this same period, the overall proportion of patients undergoing surgical resection decreased by 3.1 percentage points and radiation therapy by 6.0 percentage points, whereas chemotherapy increased 10.8 percentage points (all $P < 0.0001$). Overall average patient costs increased by $10,200 between 1998 and 2005. After controlling for changing patient demographics, lung resection rates and inpatient expenditures decreased steadily from 1998 to 2003, resulting in an 11% decrease in inpatient expenditures following the adoption of PET. Non-inpatient costs increased during the same period, largely driven by increased use of chemotherapy in advanced stage disease.

Conclusion:

The widespread adoption of PET between 1998 and 2005 for evaluation of early stage disease was accompanied by stage migration, reduced rates of lung resection, and decreased inpatient health care expenditures by 2005 after controlling for patient demographics. Over the same period, the proportion of patients undergoing chemotherapy and patients with multiple comorbidities increased, resulting in an overall increase in Medicare NSCLC patient costs. The increased use of PET in the Medicare NSCLC patient population and how it affects patient management and health care utilization remains an important area of ongoing research and evolving health policy.

7.1 Introduction

Positron emission tomography (PET) is an advanced imaging modality used in the clinical diagnosis, staging, and restaging of non-small cell lung cancer (NSCLC). Three out of the four small randomized controlled trials (RCTs) of PET use in the initial evaluation of NSCLC[1-4] have suggested that PET results in upstaging of occult metastatic NSCLC from early (I-IIIA) to late stage disease,[5] providing the potential to avoid futile resection of incurable, occult metastatic disease[2]. In privately-insured patient populations, PET has been associated with upstaging of NSCLC, [5] suggesting the potential of PET to allow patients to avoid futile thoracotomy and associated inpatient hospitalization in clinical practice outside RCTs.

We previously found evidence of PET-induced stage-migration among Medicare NSCLC patients. [6] Given the presumption that more appropriate clinical staging reduces futile local anti-neoplastic therapies, it remains an open question whether the introduction of PET within the Medicare NSCLC population was associated with decreased rates of futile local therapy and avoidable inpatient costs. In this study, we examine the treatment, health care utilization, and overall health care costs of PET use in Medicare beneficiaries with NSCLC. We test the hypotheses that the adoption of PET within the Medicare NSCLC population between 1998 and 2005 was associated with 1) a reduction in the use of surgical resection and 2) that this reduction in locally definitive treatment resulted in inpatient cost-savings and/or 3) a shift towards systemic chemotherapy.

7.2 Methods

Data Source

Data are from the Surveillance Epidemiology and End Results (SEER)-Medicare linked data. SEER-Medicare is a collaborative effort between the National Cancer Institute (NCI) and Centers for Medicare and Medicaid Services (CMS) that links routinely-collected population-based data from cancer registries across the country to Medicare administrative data and health care claims.[7] The SEER data include demographic and incident cancer characteristics including grade, and stage for approximately 25% of the U.S. cancer population. Medicare provides health insurance for 97% of Americans aged 65 and older, and these data reflect health care services used and co-morbid health conditions. SEER-Medicare data have been used previously to examine factors that affect cancer care quality including sociodemographics, physician and hospital characteristics, surgery, chemotherapy, radiation, comorbidities, complications, screening, relapse, and costs[8-18]. This study was approved by the Office of Human Research Ethics at the University of North Carolina, Chapel Hill.

Study Population

All analyses were conducted using SEER-Medicare data from the 12 SEER registries that were active from 1993 onward. Within these registries, we included all patients who had a diagnosis of cancer of the lung and bronchus with microscopically confirmed NSCLC histology between 1993 and 2005, were $\geq$ 66 years at diagnosis, and had Medicare Part A & B coverage without participating in an Health Maintenance Organization (HMO) or Medicare Part C for the year prior to and following their diagnosis or until death. We excluded patients who were diagnosed at autopsy or death or who had another diagnosis of malignancy in the year prior to their NSCLC diagnosis. We excluded patients who did not survive at least 2 months after

diagnosis to exclude clinically morbid patients for whom we expected PET use would be less likely. To help ensure full acquisition of claims for cancer-related claims, patients were required to have a primary diagnosis of lung cancer on an inpatient, outpatient, or carrier-based Medicare claim (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* diagnosis of lung cancer [162.2-162.9, 231.2]).

Study Variables

To determine patient treatment and health care costs, we used claims data on receipt of surgery, chemotherapy, radiation, and total Medicare payments from 2 months prior to 12 months following the month of NSCLC diagnosis in SEER. Receipt of each modality was ascertained using previously defined sets of HCPCS (*Health Care Procedural Coding System*) and ICD-9-CM codes (**Table 7.Supplemental**).[19,20] Receipt of surgery was defined using claims for lung resection from inpatient, outpatient, or carrier claims files.[19] Receipt of chemotherapy was defined using claims from outpatient, carrier, and durable medical equipment (DME) claims files.[20] Receipt of radiation therapy was ascertained using outpatient and carrier claims.[20]

Total patient costs were examined in the period 2 months prior to and 12 months following diagnosis in order to ensure that we captured all initial workup and treatment costs. Total Medicare payments were obtained within each claim file by summing line item payments (home health, hospice, outpatient files), total claim payment amounts (carrier and DME), or total reimbursement plus total daily per diem charges (inpatient) and adjusting all payments to 2008 dollars using the health care component of Consumer Price Indices (CPI).

Receipt of PET was detected using outpatient and carrier claims in the period 2 months prior to, and 4 months following SEER diagnosis to coincide with the 4-month follow-up period used by SEER to provide cancer stage from 1998 onward[21]. SEER-based patient zip codes and Medicare carrier claim zip codes were used to determine the straight-line distance between patients and the closest PET providing physician at the time of diagnosis.

All remaining variables were obtained from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF). Cancer stage was ascertained from SEER data and extrapolated to the American Joint Committee on Cancer (AJCC) 3rd edition staging system to provide a common staging system throughout the study period. [6] Survival at two years was obtained from the SEER-based date of death. Demographic variables included age, sex, race, ethnicity, marital status, and local census tract characteristics (metropolitan urban or rural status, percent not-finishing high school, percent below the poverty line, and percent black). Histology of NSCLC was classified as adenocarcinoma, large cell carcinoma, squamous cell, or NSCLC "otherwise undifferentiated" using the ICD-O-3 (International Classification of Disease in Oncology, 3rd Edition) code on SEER diagnosis. The 12 SEER registries included in the study were grouped according to their census regions: Northeast (Connecticut), Midwest (Detroit, Iowa), South (Atlanta, Rural Georgia), and West (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles).

Statistical Analysis

To study changes in treatment and costs over time, we defined three distinct NSCLC cohorts based on year of diagnosis that represented the pre-PET (1993-1994), initial-PET (1998-

1999), and post-PET (2004-2005) phases of PET adoption. We used comparisons between these three cohorts to assess changes in treatment patterns and costs before and after PET had become commonly used in Medicare patients. Data from the 1993-1997 years were used to detect any ongoing trends in treatment practice prior to the introduction of PET and to help to assess changes in treatment that occurred before PET. Direct comparison of 1998-1999 and 2004-2005 were made when assessing changes in practice that accompanied PET adoption and could be potentially attributed to increased PET use.

Cohort Comparisons

Treatment and cost patterns can both be heavily influenced by demographic shifts [22] and by selection bias. [23] Previous, we have observed that PET experienced rapid adoption between 1998 and 2005. [23] To capture changes in the study population over this time period, we examined demographics and patient characteristics between pre-PET, initial-PET, and post-PET cohorts composed of patients with no, little, and substantial PET use, respectively, as well as between patients who did and did not receive PET within the post-PET cohort (2004-2005). In these single variable analyses, chi-squared tests were used to compare categorical variables and Kruskal-Wallis non-parametric tests used to compare costs.

Assessment of Treatment Patterns

Multivariable logistic regression models were used to examine the use of 1) surgical resection, 2) radiation therapy, and 3) chemotherapy between 1996 and 2005 to capture changes in treatment patterns during the adoption of PET into Medicare NSCLC practice. Regression models were alternatively examined by limiting analysis to patients with early stage disease. We

hypothesized that a smaller proportion of NSCLC beneficiaries would receive surgery or radiation in the years following increased PET use in 1998. Trends in stage distribution and resection, radiation, and chemotherapy rates were plotted by year of diagnosis from 1993 through 2005 to examine temporally correlated shifts in PET use, stage migration, and treatment patterns both before and after the widespread adoption of PET among the overall Medicare NSCLC population.

Assessment of Health Care Costs

Multivariable ordinary least squares (OLS) regression models were similarly used to examine total Medicare payments within the 1) inpatient 2) non-inpatient claims, and 3) total claims files between 1996 and 2005. Medicare payments were modeled as logged costs to adjust for left-skewed cost data and to avoid non-normally distributed error terms. Relative percent differences in costs were calculated per Kennedy (1981). [24,25] Costs were alternatively modeled as costs per month survival to calculate a monthly spending rate as an alternative measure of cost. Regression analyses were run both with (not shown) and without receipt of surgery, radiation, and chemotherapy in order to analyze the impact that treatment had on observed changes in costs over time in the years after PET adoption into use. We hypothesized that following the introduction of PET in 1998 that inpatient costs would decrease secondary to decreased rates of lung resection, and that non-inpatient costs would either remain the same or increase due to increased use of chemotherapy. Inpatient, non-inpatient, and overall costs were plotted over the study period.

All regression models controlled for disease stage and patient demographics including age, race, sex, marital status, residence in a metropolitan area, region, and census tract-based

levels of local education, income, and demographic composition. In order for all observations to use sociodemographic variables from the 2000 census, 1996 was the earliest year included in regression analyses. Errors were clustered by SEER registry for all regressions [7]. Additional sensitivity analyses included the inclusion of SEER registry as a control, the removal of PET and stage interaction terms from the model to allow interpretation of PET and stage alone, and the restriction of the study cohort to 1998-2003 to limit analysis to a period during which changes in staging system occured. All results were considered significant at $P < 0.001$ unless otherwise stated in order to adjust for the considerable number of statistical tests conducted. All analyses were conducted using SAS version 9.2.

7.3 Results

Study Population

We identified 204,664 Medicare beneficiaries diagnosed with cancer of the lung and bronchus in the included SEER registries between 1993 and 2005. From these beneficiaries we identified 207,291 cases of incident lung cancer. We sequentially excluded patients (**Figure 7.1**) who were diagnosed at death or autopsy, were younger than 66 years of age, did not have microscopically-confirmed NSCLC histology, had another malignancy in the year before or after their diagnosis, participated in an HMO or did not have part A and B coverage for the year before and after their diagnosis, did not survive a minimum of 2 months from their diagnosis, did not have an prior malignancy outside of SEER, and had a Medicare claims-based ICD-9

diagnosis of lung cancer within two months prior to and four months following SEER diagnosis. The final cohort consisted of 58,575 NSCLC cases.

Comparison of Pre-PET, Initial PET, and Post-PET Cohorts

NSCLC cases differed by cohort 2005 (**Table 7.1**). In later years, NSCLC Medicare patients were composed of a larger percentage of patients older than 80, female patients, patients with comorbidities, and non-married patients (P<0.0001). Within the 2004-2005 cohort, patients who received PET were less likely to be older than age 80 (20% vs. 27%), black (7% vs. 11%), come from a census tract with less education, more poverty, or more blacks (20-22% vs. 27-28% for each), be unmarried (49% vs. 55%), or come from the Midwest (30% vs. 36%; all *P* <0.001; **Table 7.2**).

As reported previously, there was a 12-fold increase in the use of PET was observed between the initial and post-PET patient cohorts (**Table 7.3**, 5% vs. 62%, P<0.0001). The proportion of patients who resided within 40 miles of a PET providing facility increased between 1998 and 2005 due to an increase in the number of zip codes providing PET scans (62% vs. 93%). The proportion of patients alive two years after diagnosis increased from 32% in 1993 to 36% in 2005 (P<0.0001). Overall, the proportion of patients who underwent some form of treatment for their cancer was unchanged. However, there was there was a marked decrease in the proportion of NSCLC cancers that went unstaged (26% vs. 10%) and a concomitant increase in cases staged as advanced disease (40% vs. 49%). PET scans were preferentially received by patients with early stage disease (**Table 7.4**, 51% vs. 27%). Health care utilization was markedly increased among patients who underwent one or more PET scans.

Changes in Treatment Patterns

Between 1993 and 2005, a decreased proportion of patients underwent any resection (**Table 7.3**, 33% vs. 28%, P<0.0001) or radiation (56% vs. 46%, P<.0.0001). In contrast, the proportion of patients receiving chemotherapy more than doubled from 19% to 46% (P<0.0001). Total costs per patient increased from $49,384 to $56,045 between 1998 and 2005 (P<0.0001). Increasing costs were entirely driven by non-inpatient costs. The average non-inpatient cost per patient increased by approximately $7,300 between 1998 and 2005 ($20,809 vs. $28,145, P<0.0001). Inpatient costs did not exhibit a significant change in costs over the study period, but instead exhibited a trend towards decreased costs of approximately $700 between 1998 and 2005 (P = 0.02).

Among patients diagnosed in the post-PET period, patients receiving PET were more likely to undergo surgical resection (**Table 7.4**, 37% vs. 16%), chemotherapy (50% vs. 40%), and incur greater non-inpatient ($30,387 vs. $24,726) and overall health care costs ($58,115 vs. $52,890). No significant differences between patients receiving vs. not receiving PET were observed regarding utilization of radiation therapy or inpatient costs.

Between 1993 and 2005, advanced stage disease increased in frequency among the overall Medicare NSCLC population (**Figure 7.2**). The proportion of patients with advanced stage disease was stable at roughly 40% prior to the introduction of PET in 1998, after which it increased to nearly 50% by 2005. For these patients with advanced disease, surgical resection was used in less than ten percent over the study period (not shown). The frequency of early stage disease remained relatively stable over the study period, but experienced a slight increase in 2004 and 2005. The proportion of overall patients undergoing surgical resection began decreasing in 1998, but had been relatively constant in the years prior to that time. The

proportion of patients receiving radiation decreased through 1995, stabilized, and then began decreasing again in 2002. The proportion of patients receiving chemotherapy increased steadily from 1993 to 2004.

After controlling for shifting patient demographics and using 1998 as a baseline, several changes in treatment were observed (**Table 7.5**). The likelihood of a patient to undergo surgical resection steadily decreased from 2001 to 2005. The likelihood of radiation decreased over the study period, while chemotherapy use increased. Surgical resection was more likely among patients who underwent PET, had localized disease, or were married (**Table 7.5**). Surgery was less likely in elderly, uneducated, male patients with advanced stage disease or multiple comorbidities. Both radiation and chemotherapy were more likely in patients with advanced disease, and were also less likely in patients over 80 (all P <0.001).

Repeating these analyses stratifying by early vs. late stage disease (not shown) produced similar results.

Changes in Health Care Costs

Total inpatient and overall average costs per patient increased between 1993 and 2005. Total inpatient costs increased from 1993 to 1997, and then decreased beginning in 1998 (**Figure 7.2**). After controlling for shifting patient demographics and using 1998 as a baseline, several changes in healthcare costs were observed (**Table 7.6**). Average inpatient costs per patient decreased by an average of 12% by 2005 compared to 1998, after controlling for patient demographics. When surgical treatment was controlled for, inpatient costs did not experience any change over time (not shown), suggesting that changes in surgery drove decreases in inpatient expenditures. Patients located further away from PET facilities, patients older than 80,

and patients in the South had decreased inpatient expenditures compared with their counterparts in the West. Increased inpatient expenditures were associated with black race, localized disease, comorbidities, and lower education attainment (all $P < 0.001$). Non-inpatient costs increased from 2002 onward and were elevated in patients with comorbidities or who were married. Non-inpatient costs were also elevated in patients receiving PET or with advanced disease in models excluding PET x stage interaction terms (not shown). Total costs per patient did not change significantly between 1998 and 2005 after controlling for patient demographics.

Analyses of costs were repeated using cost per month of survival (**Table 7.7**). Results were overall similar, except that PET was associated with reduced inpatient costs per month. This is likely an effect of selection bias, whereby patients who received PET were more to live longer and have lower costs per month since costs were spread out over a longer period. Similarly, advanced stage disease was associated with per month increased spending across inpatient, non-inpatient, and total health care expenditures per month, likely as a result of shorter survival times. The analysis may be limited with regardless to examining costs per unit time since only one year of claims are examined for health care expenditures in this study.

Inpatient, non-inpatient, and overall costs did not change over time after controlling for patient receipt of surgery, radiation, or chemotherapy. Receipt of surgery was associated with an 88% increase in inpatient expenditures and only a 6% increase in non-inpatient costs, whereas receipt of chemotherapy was associated with a 97% increase in non-inpatient costs and no change in inpatient expenditures. Radiation therapy was associated with an 12% increase in inpatient and 26% increase in outpatient patient expenditures. For overall costs, use of surgery (48%), radiation (20%), or chemotherapy (34%) each resulted in increased total health care expenditures (all $P < 0.0001$).

Sensitivity Analysis

To examine whether cost analyses were sensitive to the time window, we performed separate sensitivity analysis using a 2-year, rather than a 1-year, cost window. Inpatient, non-inpatient, and overall costs summed over two years were approximately 15-25% greater than costs summed over one year. Both univariate and multivariable analyses using 2-year vs. 1-year costs yielded qualitatively similar results. Additional sensitivity analyses including SEER region, excluding interaction effects, and limited to 1998-2003 all yielded qualitatively similar findings as the main analysis.

7.4 Discussion

After controlling for shifting demographics, we found that patients were less likely to receive surgery and have lower inpatient costs in the years following the adoption of PET in the Medicare NSCLC population. During the same time period total and non-inpatient costs increased. Because of bidirectional associations between PET and stage, demonstrating a direct association of PET with reduced thoracotomies is difficult using a non-experimental approach. Nonetheless, this study provides evidence that PET-induced stage migration may have reduced rates of futile thoracotomy resulting in subsequent inpatient health care savings. However, during the same period, the use of chemotherapy and non-inpatient expenditures increased rapidly, offsetting potential savings in inpatient expenditures. Estimates from 2003-2005 suggest a relatively stable reduction of 11% in inpatient expenditures, which in 2005 would have

amounted to roughly $2,800 savings per patient. Accounting for the average cost of a PET scan during the same period ($1,400) suggests that the introduction of PET into the Medicare NSCLC may have saved roughly $1,400 per diagnosis in inpatient costs. During the same time period, these potential inpatient cost savings were offset by increased non-inpatient costs of 15%-22%, more than enough to counteract any inpatient cost savings. This increased non-inpatient cost appears to have occurred largely as a result of increased chemotherapy use, which began to include the use of dual vs. single agent chemotherapy per the American Society of Clinical Oncologist (ASCO) 2003 guidelines. [26]

One large private California insurer[5] and three out of four small randomized controlled trials (RCTs)[1-4] have suggested that PET may result in upstaging of occult metastatic NSCLC from early to late stage disease,[5] with most studies finding a reduction in futile thoracotomies of one half, similar to the odds ratios we estimated in our study. Assuming a similar effect size in our study and a historic rate of early stage disease of roughly 60% would predict a decrease in overall surgical resection of approximately 4%, comparable to 3.4% reduction we observed between the 1998-1999 and 2004-2005 cohorts. To date, no randomized trial of PET staging has demonstrated any trend towards decreased mortality.[1-4]

Despite stable or decreasing inpatient costs, overall health care costs increased by an average of $10,300 per patient between 1993-1994 and 2004-2005. We previously reported an average increase in overall imaging costs of $1,500 per patient between 1999 and 2004 [27], which would leave an unexplained increase in overall costs of $8,800. Increased costs between 1993 and 2005 coincided with a substantial increase in the proportion of patients undergoing chemotherapy and the proportion of patients with multiple comorbidities, both of which were associated with substantial increases in total health care costs. Randomized trials of PET use in

NSCLC have been accompanied by cost-effectiveness analyses attempting to capture PET-associated savings from reduced rates of futile thoracotomies. [1] PET can be used to avoid these futile thoracotomies, which might otherwise occur when a patient presents with occult metastatic disease undergoes local, definitive treatment for an incurable disease. Our results suggest that although the introduction of PET may have reduced the number of futile thoracotomies, it may have also inadvertently led to the increased use of chemotherapy and observed increase in overall Medicare spending. Although we did not analyze the cost of chemotherapy directly in our study, the ASCO-recommended use of doublet chemotherapy in 2003 would certainly increase material costs of chemotherapy compared with a single agent. This shift in care from thoracotomy to chemotherapy has not previously been appreciated within small randomized trials and represents an important consideration when evaluating the overall effect of PET use on health care expenditures. Continuing evaluation of the effect of PET on overall cancer patient evaluation, management, and outcomes will likely be aided in the future by the continued implementation of national, prospective databases of PET use such the National Oncologic PET Registry (NOPR).[28-30]

There are many questions that arise in response to our study findings that may warrant further research. The increased use of PET and its role in clinical decision making and its use, timing, and value in conjunction with other diagnostic and evaluative tests is not fully understood. How patient performance status affects the likelihood of receiving PET might help provide a more accurate model of how performance status affects imaging use and how these factors might impact attempts to legislate changes in health care reform. A PET-induced shift in care from thoracotomy to chemotherapy has not previously been appreciated within small randomized trials and represents an important consideration when evaluating the overall effect of

PET use on health care expenditures. Future studies examining how PET directly augments or alters the use of chemotherapy or alternative treatments could provide valuable insight into cost-drivers of the rapidly increasing chemotherapy-rich landscape of treatment. The emergence of molecularly-targeted therapies occurred largely after the time frame analyzed by this study, and will almost certainly alter how PET use changes both the approach to treatment and costs of NSCLC in the future.

Limitations

This study has several limitations as a retrospective, claims-based analysis. Only PET scans paid for by Medicare could be detected in our analysis. In order to minimize the proportion of missed claims, all analyses were limited to Medicare beneficiaries with both Part A and B coverage and no HMO participation or Part C coverage for the 12 months prior to and following their diagnosis. Patients within the SEER registry are overall more likely to be non-, live in non-poverty areas, and live in urban areas. [7] Medicare claims include IV chemotherapy and oral equivalents, but do not include chemotherapy or supportive medications filled as outpatient prescription drugs and were not captured in this study. Oral chemotherapy can pose a substantial cost to patients and outside insurers, and our analysis likely underestimates the overall costs to cancer patients. Two examples of oral chemotherapy agents used in the treatment of lung cancer include etoposide and tarceva, which were not observed in this study but are often administered in the palliative setting.[26,31] Because of a largely palliative role of these agents, their use may be specifically increased by PET-induced stage migration. Future studies to examine more specifically how PET affects patient management and chemotherapy

selection provide a value avenue of future research. The most recent year of diagnosis examined in this study was 2005, which is the most recent SEER cohort available for which two full years of survival follow-up were available to determine 2-yr survival. Our analysis of distance between patient residence and PET providing facilities was based on distances between zip code centroids as a surrogate for travel time [32].

Conclusions

We found that surgical resection and corresponding inpatient costs decreased in the NSCLC Medicare patient population following the widespread adoption of PET. This study and previous work[2,5] supports a role for PET in the upstaging of early stage NSCLC patients and corresponding reduction in futile attempts at local control of occult metastatic disease. Inpatient savings associated with the adoption of PET may have been offset by increased rates of non-inpatient chemotherapy used to preferentially treat advanced stage disease. The ability of PET to affect patient management, health care utilization, and costs remain important areas of ongoing research that may change as new treatments become available in the future.

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Table 7.1 – Case Demographics by PET Diffusion Cohort

Characteristic	Year of Diagnosis			P-Value
	Pre-PET (1993-1994) N = 8,837	Initial PET (1998-1999) N = 8,017	Post-PET (2004-2005) N = 10,436	
Age > 80, No. (%)	1287 (14.6)	1460 (18.2)	2342 (22.4)	<.0001
Male, No. (%)	5111 (57.8)	4416 (55.1)	5312 (50.9)	<.0001
Black, No. (%)	672 (7.6)	670 (8.4)	862 (8.3)	0.14
Comorbid conditions, No. (%)				<.0001
0	5404 (61.2)	4514 (56.3)	5186 (49.7)	
1	2283 (25.8)	2185 (27.3)	3071 (29.4)	
2+	1150 (13)	1318 (16.4)	2179 (20.9)	
2000 Census Tract Demographics: (Highest Quartile)				
Did not complete high school	---	1687 (25.8)	2135 (23)	0.0002
Percent below poverty line	---	1704 (26.1)	2156 (23.3)	<.0001
Percent black	---	1608 (24.6)	2211 (23.8)	0.25
Married (%)	5024 (56.9)	4533 (56.5)	5496 (52.7)	<.0001
Metropolitan (%)	7748 (87.7)	6819 (85.1)	8977 (86)	<.0001
Region				<.0001
West	3894 (44.1)	3464 (43.2)	4749 (45.5)	
Midwest	2920 (33)	2847 (35.5)	3376 (32.4)	
Northeast	1417 (16)	1156 (14.4)	1626 (15.6)	
South	606 (6.9)	550 (6.9)	685 (6.6)	

PET: positron emission tomography

Table 7.2 – Case Characteristics by PET use within 2004-2005 Cohort

Characteristic	NO PET (N = 4,133)	PET (N = 6,303)	P-Value
Age > 80, No. (%)	1101 (26.6)	1241 (19.7)	<.0001
Male, No. (%)	2127 (51.5)	3185 (50.5)	0.35
Black, No. (%)	452 (10.9)	410 (6.5)	<.0001
Comorbid conditions, No. (%)			0.19
0	2044 (49.5)	3142 (49.9)	
1	1191 (28.8)	1880 (29.8)	
2+	898 (21.7)	1281 (20.3)	
2000 Census Tract Demographics: (Highest Quartile)			
Did not complete high school	1014 (27.5)	1121 (20.1)	<.0001
Percent below poverty line	1029 (27.9)	1127 (20.2)	<.0001
Percent black	990 (26.8)	1221 (21.9)	<.0001
Married (%)	2026 (49)	3470 (55.1)	<.0001
Metropolitan (%)	3531 (85.4)	5446 (86.4)	0.16
Region			<.0001
West	1876 (45.4)	2873 (45.6)	
Midwest	1503 (36.4)	1873 (29.7)	
Northeast	493 (11.9)	1133 (18)	
South	261 (6.3)	424 (6.7)	

PET: positron emission tomography

Table 7.3 – Univariate Outcomes, Treatment, and Costs by PET Diffusion Cohort

Characteristic	Year of Diagnosis			P-Value
	Pre-PET (1993-1994) N = 8,837	Initial PET (1998-1999) N = 8,017	Post-PET (2004-2005) N = 10,436	
Any PET scans, No. (%)	0 (0)	380 (4.7)	6303 (60.4)	<.0001
Distance to PET < 40 miles, No. (%)	0 (0)	4942 (61.6)	9708 (93)	<.0001
Stage, No. (%)				<.0001
Localized Disease (I-IIIA)	3060 (34.6)	2865 (35.7)	4333 (41.5)	
Advanced Stage Disease (IIIB-IV)	3483 (39.4)	3492 (43.6)	5059 (48.5)	
Unstaged	2294 (26)	1660 (20.7)	1044 (10)	
Overall 2-yr Survival, No. (%)	2809 (31.8)	2703 (33.7)	3709 (35.5)	<.0001
Treatment				
Any Resection, No. (%)	2923 (33.1)	2518 (31.4)	2956 (28.3)	<.0001
Any Radiation, No. (%)	4954 (56.1)	4126 (51.5)	4744 (45.5)	<.0001
Any Chemotherapy, No. (%)	1670 (18.9)	2819 (35.2)	4805 (46)	<.0001
No Treatment, No. (%)	1449 (16.4)	1271 (15.9)	1855 (17.8)	0.0013
Costs (Mean, 2008 dollars)				
Inpatient	$27,410	$28,575	$27,900	.02
Non-inpatient	$18,324	$20,809	$28,145	<.0001
PET *	$0	$39	$842	<.0001
Total	$45,734	$49,384	$56,045	<.0001

*PET costs are a subset of non-inpatient costs. PET: positron emission tomography

Table 7.4 – Univariate Outcomes, Treatment, and Costs by Receipt of PET

Characteristic	NO PET (N = 4,133)	PET (N = 6,303)	P-Value
Distance to PET < 40 miles, No. (%)	3817 (92.4)	5891 (93.5)	0.03
Stage, No. (%)			<.0001
Localized Disease (I-IIIA)	1100 (26.6)	3233 (51.3)	
Advanced Stage Disease (IIIB-IV)	2500 (60.5)	2559 (40.6)	
Unstaged	533 (12.9)	511 (8.1)	
Overall 2-yr Survival, No. (%)	911 (22)	2798 (44.4)	<.0001
Treatment			
Any Resection, No. (%)	658 (15.9)	2298 (36.5)	<.0001
Any Radiation, No. (%)	1819 (44)	2925 (46.4)	0.02
Any Chemotherapy, No. (%)	1626 (39.3)	3179 (50.4)	<.0001
No Treatment, No. (%)	1140 (27.6)	715 (11.3)	<.0001
Costs (Average, 2008 dollars)			
Inpatient	$28,164	$27,728	0.04
Non-inpatient	$24,726	$30,387	<.0001
PET *	$0	$1,394	<.0001
Total	$52,890	$58,115	<.0001

*PET costs are a subset of non-inpatient costs. PET: positron emission tomography

Table 7.5 – Regression Analysis of Receiving Any Resection, Radiation, or Chemotherapy between 1996 and 2005 (N=38,359)

Characteristic	Any Resection OR (95% CI)	Any Radiation OR (95% CI)	Any Chemo OR (95% CI)
Year of Diagnosis			
1996	1.01 (0.88-1.16)	1.09 (1-1.19)	0.67 (0.61-0.74)*
1997	1.03 (0.94-1.13)	1.05 (0.92-1.19)	0.83 (0.75-0.92)*
1998 (Reference)	---	---	---
1999	1.07 (0.95-1.21)	0.96 (0.88-1.04)	1.14 (1.01-1.28)
2000	0.95 (0.86-1.05)	0.98 (0.9-1.06)	1.23 (1.11-1.36)*
2001	0.77 (0.68-0.87)*	0.92 (0.81-1.04)	1.18 (1.03-1.35)
2002	0.67 (0.6-0.75)*	0.76 (0.67-0.86)*	1.21 (1.03-1.41)
2003	0.6 (0.55-0.65)*	0.69 (0.62-0.78)*	1.3 (1.16-1.46)*
2004	0.5 (0.46-0.55)*	0.65 (0.57-0.76)*	1.55 (1.32-1.81)*
2005	0.49 (0.46-0.53)*	0.61 (0.52-0.71)*	1.42 (1.21-1.66)*
Any PET	1.79 (1.49-2.14)*	1.56 (1.36-1.79)*	1.55 (1.42-1.69)*
Localized Disease	6.49 (5.27-8)*	0.64 (0.58-0.71)*	0.45 (0.39-0.52)*
Advanced Stage	0.27 (0.22-0.34)*	1.61 (1.44-1.79)*	1.5 (1.37-1.65)*
Localized x PET	0.95 (0.82-1.11)	0.98 (0.87-1.12)	1.04 (0.88-1.23)
Advanced x PET	1.77 (1.53-2.04)*	0.94 (0.81-1.1)	1.14 (0.99-1.32)
PET > 40 miles away	0.95 (0.86-1.06)	1.05 (0.95-1.16)	1 (0.87-1.16)
Age >80	0.47 (0.43-0.51)*	0.84 (0.8-0.89)*	0.36 (0.34-0.38)*
Black	0.7 (0.63-0.78)*	1.13 (1.02-1.24)	1 (0.9-1.12)
Comorbidities			
One	0.91 (0.84-1)	0.97 (0.94-1.01)	0.89 (0.86-0.93)*
Multiple	0.74 (0.68-0.81)*	0.96 (0.92-1)	0.65 (0.6-0.72)*
Census tract:% Education < 12 years			
2nd QRTL	0.8 (0.72-0.9)*	1.07 (1.02-1.12)	1.02 (0.99-1.05)
3rd QRTL	0.76 (0.63-0.9)	1.05 (0.98-1.13)	1 (0.91-1.1)
4th QRTL	0.71 (0.6-0.86)*	1.08 (0.99-1.18)	1 (0.87-1.15)
Census tract:% Below Poverty Line			
2nd QRTL	1.04 (0.95-1.14)	0.95 (0.89-1.02)	0.93 (0.89-0.98)
3rd QRTL	1.04 (0.93-1.16)	0.91 (0.85-0.98)	0.86 (0.79-0.92)*
4th QRTL	0.99 (0.86-1.14)	0.95 (0.87-1.03)	0.79 (0.66-0.95)
Census tract:% Black			
2nd QRTL	1.04 (0.98-1.1)	1.01 (0.95-1.08)	1.02 (0.96-1.08)
3rd QRTL	1 (0.9-1.13)	1.02 (0.95-1.09)	1.05 (0.97-1.13)
4th QRTL	1.12 (1.03-1.22)	0.97 (0.89-1.06)	0.94 (0.84-1.04)
Male	0.74 (0.7-0.78)*	1.2 (1.14-1.26)*	1.2 (1.13-1.28)*
Married (%)	1.33 (1.27-1.4)*	1.05 (1.01-1.09)	1.36 (1.29-1.42)*
Metropolitan (%)	1.05 (0.91-1.2)	0.96 (0.86-1.07)	1.02 (0.83-1.25)
Region			
Midwest	1 (0.81-1.24)	1.22 (1.14-1.31)*	1.1 (0.87-1.39)
Northeast	1.13 (0.9-1.41)	1.07 (1-1.15)	1.12 (0.98-1.29)
South	0.83 (0.65-1.05)	1.17 (1.05-1.3)	1.51 (1.3-1.77)*

*P<0.001; Abbreviations: OR, Odds Ratio; PET, positron emission tomography; QRTL, quartile, CI, confidence interval

Table 7.6 – Regression Analysis of Inpatient, Non-Inpatient, and Total Costs between 1996 and 2005 (N=38,359)

Characteristic	Inpatient Relative Δ % Cost (95% CI)†	Non-Inpatient Relative Δ % Cost (95% CI)†	Total Relative Δ % Cost (95% CI)†
Year of Diagnosis			
1996	-1.5 (-9, 6.7)	-3.6 (-6.9, -0.1)	-2.0 (-7.5, 3.8)
1997	-4.3 (-10.7, 2.5)	-2.6 (-6.3, 1.2)	-3.3 (-8.6, 2.3)
1998 (Reference)	---	---	---
1999	-3.8 (-6.3, -1.2)	0.6 (-3, 4.5)	-1.8 (-4, 0.5)
2000	-9.7 (-13.3, -5.8)*	1.0 (-2.7, 4.9)	-5.2 (-9.2, -1.1)
2001	-9.1 (-13.9, -4)*	6.6 (2, 11.3)	-2.5 (-7.3, 2.6)
2002	-6.0 (-11.3, -0.4)	9.1 (4.7, 13.7)*	0.0 (-4.2, 4.5)
2003	-10.7 (-15.7, -5.3)*	18.2 (11.4, 25.5)*	1 (-4.3, 6.7)
2004	-11.2 (-18.8, -3)	22 (16.6, 27.6)*	2.4 (-4.2, 9.5)
2005	-11.9 (-16.3, -7.3)*	14.6 (8.4, 21.1)*	-1.1 (-6.2, 4.2)
Any PET	-3.5 (-12.5, 6.6)	24.9 (18.8, 31.2)*	11.2 (5, 17.7)*
Localized Disease	29.8 (25.3, 34.3)*	-14.7 (-17.7, -11.6)*	9.4 (7.2, 11.7)*
Advanced Stage	6.7 (-1.6, 15.7)	4.5 (2.1, 7)*	5.4 (1.2, 9.7)
Localized x PET	6.6 (0.5, 13)	-2.3 (-6.5, 2)	-1.4 (-4.9, 2.3)
Advanced x PET	-0.5 (-8.5, 8.2)	3.9 (-0.6, 8.5)	1.9 (-4, 8.3)
PET > 40 miles away	-15.2 (-22.3, -7.4)*	-3.0 (-7.8, 2.1)	-9.8 (-16.1, -2.9)
Age >80	-14.6 (-17.5, -11.6)*	-19.6 (-20.4, -18.8)*	-16.6 (-18.7, -14.5)*
Black	19.4 (11.2, 28.2)*	4.1 (-0.6, 9.1)	12.9 (6.9, 19.2)*
Comorbidities			
One	11.1 (8, 14.4)*	4.9 (2.3, 7.6)*	8.4 (6.1, 10.8)*
Multiple	34.7 (28.5, 41.2)*	10.3 (5.1, 15.7)*	24.2 (18, 30.8)*
Census tract:% Education < 12 years			
2nd QRTL	0.7 (-3.4, 4.9)	0.1 (-3.6, 4)	0.7 (-2.9, 4.4)
3rd QRTL	5.1 (-0.4, 10.9)	-0.1 (-6.2, 6.4)	2.7 (-2.8, 8.4)
4th QRTL	16.1 (7.6, 25.4)*	2.7 (-4.3, 10.2)	10.0 (3.2, 17.3)
Census tract:% Below Poverty Line			
2nd QRTL	-2.3 (-4.6, 0.1)	-2.9 (-5.8, 0)	-2.6 (-4.9, -0.2)
3rd QRTL	-4.1 (-10.8, 3.1)	-5 (-10.2, 0.4)	-4.8 (-10.6, 1.4)
4th QRTL	0.5 (-11.4, 14)	-6.5 (-16.1, 4.1)	-2.3 (-13.4, 10.1)
Census tract:% Black			
2nd QRTL	2.6 (-1, 6.4)	0.3 (-2.6, 3.2)	1.6 (-0.7, 4.1)
3rd QRTL	6.8 (2, 11.8)	3.1 (-1.3, 7.6)	5.2 (2.1, 8.5)
4th QRTL	5.7 (-1.3, 13.2)	2 (-4, 8.3)	4.3 (-1.8, 10.8)
Male	4.1 (1.5, 6.7)	-0.2 (-2.1, 1.7)	2.1 (0, 4.3)
Married (%)	-5.2 (-8.4, -1.9)	7.3 (5.6, 9.1)*	0.2 (-2.5, 3)
Metropolitan (%)	24.1 (9, 41.4)	11 (1.5, 21.4)	17.1 (6.6, 28.7)*
Region			
Midwest	-15.3 (-31.1, 4.2)	1.2 (-11.9, 16.3)	-7.4 (-21.8, 9.7)
Northeast	-4.4 (-18.6, 12.2)	4.1 (-0.4, 8.8)	-0.4 (-10.6, 10.9)
South	-27.8 (-39.2, -14.3)*	2.0 (-2.8, 7)	-15.1 (-24.4, -4.6)

*P<0.001; Abbreviations: PET, positron emission tomography; QRTL, quartile, CI, confidence interval.

† Relative Δ % Cost = Relative Percent Change in Costs = $\text{Exp}(\beta - \frac{1}{2}\sigma_\beta^2) - 1$ (per Kennedy 1981).

Table 7.7 – Regression Analysis of *Monthly* Inpatient, Non-Inpatient, and Total Costs between 1996 and 2005 (N=38,359) in the first 12 months following diagnosis

Characteristic	Inpatient Relative Δ % Cost (95% CI)†	Non-Inpatient Relative Δ % Cost (95% CI)†	Total Relative Δ % Cost (95% CI)†
Year of Diagnosis			
1996	-2.1 (-7.9, 4)	-3.9 (-6.7, -1)	-2.7 (-6.6, 1.4)
1997	-3.1 (-7.7, 1.7)	-2.7 (-5.3, 0)	-2.8 (-6.2, 0.7)
1998 (Reference)	---	---	---
1999	-4.7 (-10.7, 1.7)	-1.1 (-4.3, 2.2)	-3.1 (-7, 0.9)
2000	-9.3 (-12.4, -6)*	-0.5 (-3.3, 2.4)	-5.8 (-8.7, -2.8)*
2001	-4.7 (-8.9, -0.3)	6.6 (3.3, 10)*	-0.3 (-3.9, 3.4)
2002	0.1 (-6.4, 7.1)	10.1 (6.7, 13.7)*	3.7 (0, 7.5)
2003	-5.3 (-9.5, -0.8)	18.4 (12.3, 24.9)*	3.8 (-0.2, 7.9)
2004	-5.5 (-11.5, 0.8)	23 (18.2, 27.9)*	5.6 (0.9, 10.5)
2005	-2.8 (-7.2, 1.9)	17.5 (12.6, 22.7)*	4.9 (1.3, 8.6)
Any PET	-20.6 (-29, -11.1)*	10.8 (6.9, 14.9)*	-5.6 (-11.1, 0.3)
Localized Disease	14.4 (9.4, 19.6)*	-21.3 (-24, -18.5)*	-0.9 (-2.9, 1.1)
Advanced Stage	30.4 (20.7, 40.9)*	21.1 (18.4, 23.8)*	26.1 (20.6, 31.8)*
Localized x PET	16.6 (6.7, 27.5)*	2.5 (-1.3, 6.5)	6.1 (0.9, 11.6)
Advanced x PET	-3.7 (-11.7, 5)	-0.9 (-4.8, 3.1)	-3.0 (-8.3, 2.6)
PET > 40 miles away	-18.3 (-25.9, -9.8)*	-4.0 (-8.7, 0.9)	-12.1 (-18.8, -4.9)
Age >80	-9.1 (-12.6, -5.4)*	-14.3 (-15.6, -13.1)*	-11.2 (-13.8, -8.4)*
Black	20.2 (13.3, 27.6)*	1.6 (-2.7, 6.2)	12.7 (7.3, 18.3)*
Comorbidities			
One	13.6 (8.4, 19)*	5.3 (3.1, 7.6)*	10.0 (6.4, 13.8)*
Multiple	41.9 (35.2, 48.9)*	14.7 (9.8, 19.8)*	30.7 (24.5, 37.3)*
Census tract:% Education < 12 years			
2nd QRTL	1.7 (-1.7, 5.2)	0.1 (-2.8, 3.1)	1.3 (-1.7, 4.3)
3rd QRTL	7.9 (2.2, 13.9)	0.5 (-4.8, 6.1)	4.6 (-0.5, 10)
4th QRTL	22.1 (12.1, 32.9)*	4 (-2, 10.4)	14 (6.9, 21.6)*
Census tract:% Below Poverty Line			
2nd QRTL	-3.4 (-6.2, -0.5)	-3.6 (-6.2, -1)	-3.6 (-5.9, -1.1)
3rd QRTL	-6.5 (-13.6, 1.2)	-5.7 (-11, -0.1)	-6.4 (-12.3, 0)
4th QRTL	-0.3 (-13.8, 15.4)	-7.4 (-16.5, 2.7)	-3.1 (-14.7, 10.2)
Census tract:% Black			
2nd QRTL	2.9 (-1.8, 7.8)	0.6 (-2.1, 3.4)	1.9 (-1, 4.9)
3rd QRTL	9.3 (3.8, 15.1)*	3.7 (-0.4, 7.9)	6.9 (3.5, 10.5)*
4th QRTL	6.6 (-2.8, 16.9)	2.9 (-3.3, 9.4)	5.4 (-1.8, 13.2)
Male	8 (5.5, 10.7)*	3.7 (1.6, 5.8)*	6.3 (3.8, 8.8)*
Married (%)	-8.5 (-11.2, -5.7)*	4.3 (2.5, 6.1)*	-3.3 (-5.8, -0.7)
Metropolitan (%)	25.9 (9.1, 45.4)	11.4 (2.7, 20.9)	18.5 (7.4, 30.6)*
Region			
Midwest	-17.1 (-32.9, 2.3)	1 (-11.1, 14.8)	-9.1 (-23.4, 7.9)
Northeast	-8.9 (-23.1, 7.9)	1.6 (-3.3, 6.8)	-4.3 (-15.2, 7.9)
South	-29.5 (-40.9, -15.9)*	2.4 (-2.7, 7.8)	-16.8 (-26.6, -5.7)

*P<0.001; Abbreviations: PET, positron emission tomography; QRTL, quartile, CI, confidence interval.

† Relative Δ % Cost = Relative Percent Change in Costs = $\text{Exp}(\beta - \frac{1}{2}\sigma_\beta^2) - 1$ (per Kennedy 1981).

Table 7.Supplemental – HCPCS and ICD-9-CM codes used to detect surgical resection, chemotherapy, and radiotherapy

Treatment Modality	Claims Files	Codes
Surgery (Lung Resection)	Inpatient Outpatient Carrier	HCPCS 31766, 32440, 32442, 32445, 32480, 32484, 32485, 32486, 32488, 32500, 32520, 32522, 32525, 32657, 32663 ICD-9-CM 32.29, 32.3-32.99
Chemotherapy	Outpatient Carrier DME	HCPCS 95549, 96400, 96404, 96406, 96410, 96412, 96414, 96420, 96422, 96423, 96425, 96440, 96445, 96450, 96542, 96545, C9017, J0182, J8510, J8530, J8560, J8610, J899, J9000, J9001, J9010, J9045, J9060, J9062, J9070, J9080, J9090-J9097, J9170, J9180-J9182, J9190, J9201, J9206, J9208, J9230, J9250, J9260, J9265, J9280, J9290, J9291, J9350, J9360, J9370, J9375, J9380, J9390, J9999, Q0083, Q0084, Q0085, Q0125, Q0127-Q0129, S0178, S0182, S9329, S9330, S9331
Radiation Therapy	Outpatient Carrier	HCPCS 31643, 77300, 77301, 77305, 77310, 77315, 77321, 77326, 77327, 77328, 77331-77334, 77336, 77370, 77380, 77381, 77399, 77401-77404, 77406-77409, 77411-77414, 77416-77420, 77425, 77427, 77430-77432, 77470, 77499, 77520, 77522, 77523, 77525, 77750, 77761-77763, 77781-77784, 77799, C1716-C1720, C1790-C1806, C2616, G0126, G0173

HCPCS: Healthcare Common Procedure Coding System
ICD-9 CM: International Classification of Diseases – 9th edition – Clinical Modification
DME: Durable Medical Equipment

Figure 7.1: CONSORT diagram.

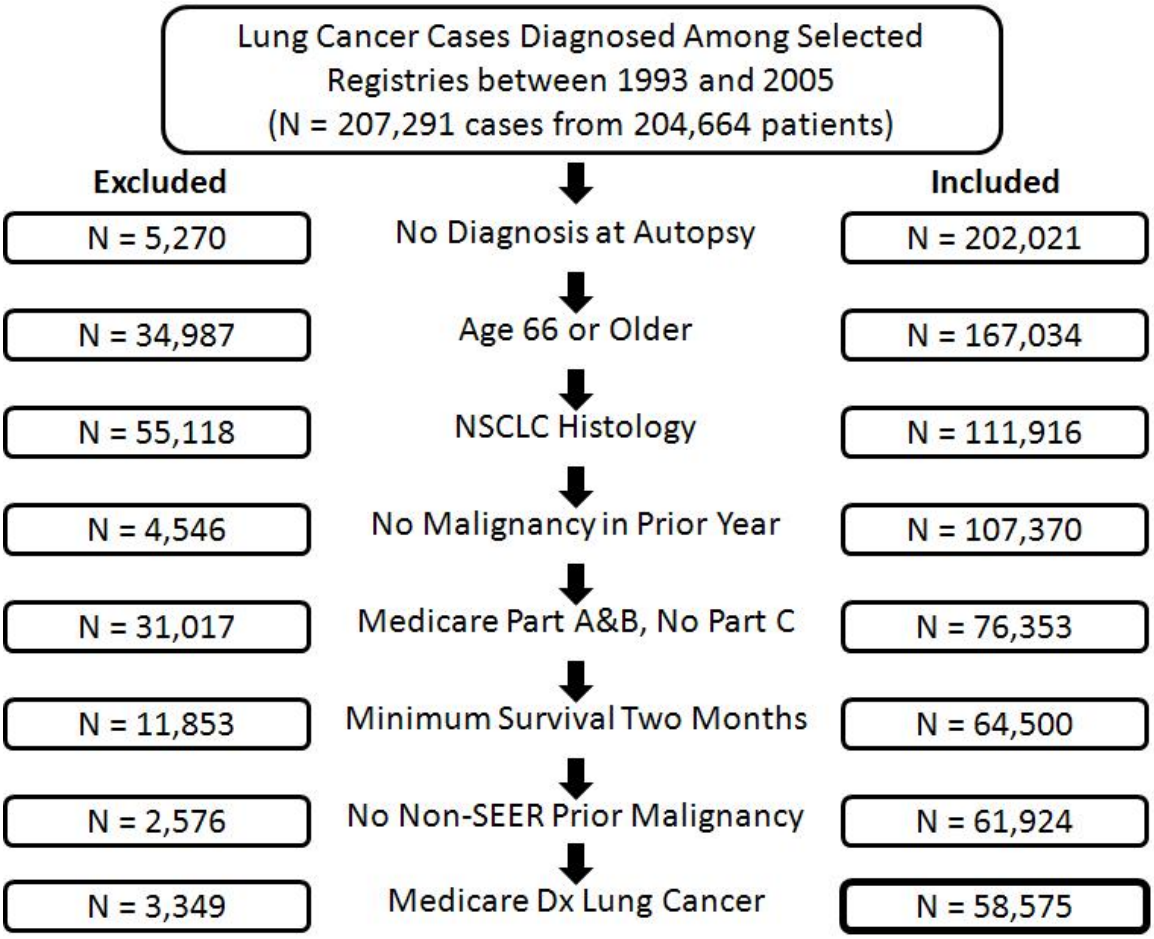
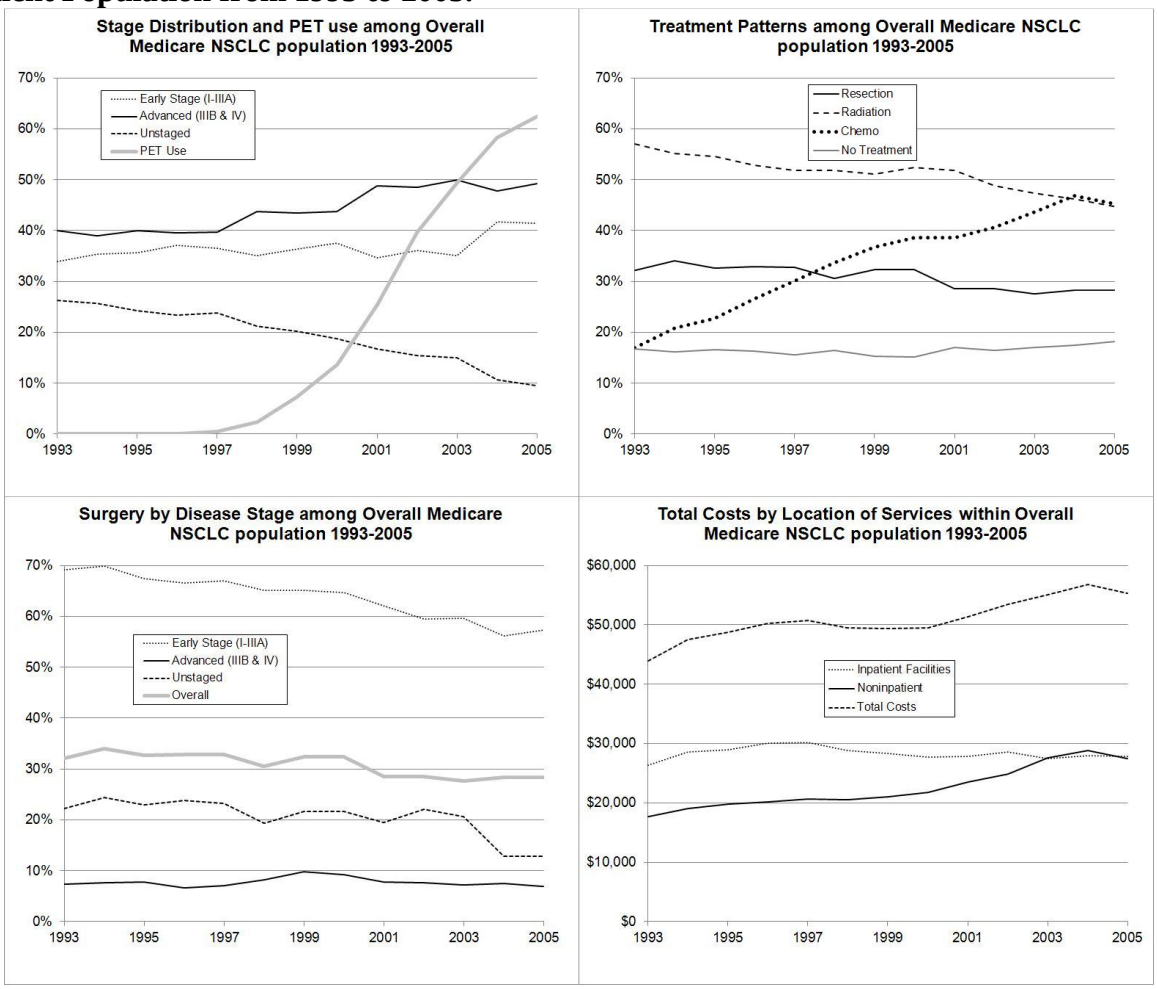


Figure 7.2: Stage Distribution, Treatment, and Costs of the overall NSCLC Medicare Patient Population from 1993 to 2005.



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CHAPTER 8: DISCUSSION

Overview

Positron Emission Tomography (PET) is an advanced imaging modality that began to be used to differentiate malignant and benign solitary pulmonary nodules in 1992[1] and was initially approved for this use by Medicare in 1998[2]. Since then, PET utilization has increased in clinical practice among both Medicare and privately-insured NSCLC patients[3,4], with Medicare lung cancer beneficiaries receiving an average of one PET scan per patient by 2006[3]. Overall incidence of lung cancer among Americans older than age 65 is an order of magnitude higher than it is for younger individuals[5], making NSCLC outcomes among the elderly an important topic of ongoing research. Remarkably little is known about how PET affects Medicare NSCLC patient treatment, outcomes, and health care costs. In this dissertation I explored how the rapid expansion of PET use within Medicare patients affected the access, quality, and care of NSCLC patients.

8.1 Study 1: Demographic Variation in the use of PET in Medicare NSCLC

Previous work suggests that the rapid expansion of PET may have occurred non-uniformly throughout the NSCLC patient population following the national coverage decision by Medicare in 1998. [6,7] Such discrepancies in delivery of technology could have had considerable implications with regards to quality, access, and care, and are particularly concerning from the

perspective of a public insurer that must balance health care needs and expenditures on a nationwide scale.

This study found that PET utilization among NSCLC patients increased following its approval by Medicare in 1998, reaching a utilization rate of 50% or more by 2005 regardless of race, age, region, or local census characteristics. Despite widespread adoption of PET overall, patients who were older, black, or from less educated or more impoverished census tracts had lower utilization of PET that persisted through 2005, with an absolute decrease in PET utilization of approximately ten percentage points within each group. Expansion of PET occurred preferentially within the Northeast following Medicare expansion of PET indications for the diagnosis, staging, and restaging of NSCLC in 2001. Contrary to our hypothesis that unequal utilization of PET would decrease with increasing PET availability, we found that differences in PET utilization rates persisted among sociodemographic and regional subgroups through 2005. Specifically, PET use was higher for non-blacks, patients under the age of 80, and patients living in the Northeast. Whether persistently disparate PET use represented underutilization or overutilization is unclear.

On July 1 2001, PET was approved for the diagnosis, initial staging, and restaging of NSCLC. This national coverage determination should in theory have equally affected the adoption of PET use in NSCLC nationwide. However, between 2001 and 2002, the Northeast (Connecticut) registry increased its use of PET significantly faster than all other registries. It has been previously shown that the introduction of new technology often occurs heterogeneously during the early phases of growth[7 8 9]. Our results suggest that introduction of national coverage policies may also introduce potential sources of increased heterogeneous use of existing technology. A potential policy implication of this would be to increase efforts to promote equal

dissemination of services among Medicare patients following expansion of any Medical service, not just new or emerging technology.

Possible explanations for disparate use of PET include differences in the availability of technology, cost, physician preference, and patient preference. Disparities in race, gender, and age have been observed with regards to cancer health care access, treatment, and survival [10-28], particularly with regards to receiving new or higher-technology services [11]. Our analysis suggests that reduced access to PET as a result of distance from PET facilities had largely disappeared by 2005. Whether this disappeared as a result of social networking, changes in general knowledge, or aggressive marketing is not known. Understanding how the effect of distance has been mitigated in the receipt of NSCLC PET could provide insight into how we might be able to neutralize unequal utilization of other limited health care resources.

8.2 Study 2: PET-induced stage migration and selection bias among Medicare NSCLC patients

The use of PET and PET/CT was covered by Medicare because of its ability to more sensitive and specific staging and evaluation of NSCLC compared with CT alone[29]. PET use was rapidly adopted within the Medicare NSCLC population following its approval by CMS. Early observational studies had reported an association between PET and superior NSCLC patient outcomes in Medicare beneficiaries[4] and one large privately insured California population[30]. However, such findings could have been biased if PET was selectively administered to populations with greater access to health care. Specifically, if observational data suggest that early detection via PET could improve survival, it is possible that this benefit could

be an artifact of upstaging, rather than a true improvement in survival. This concern prompted our second study, which investigated 1) if PET improved outcomes and 2) if not, why had a survival benefit been observed by previous epidemiologic studies.

We found that despite widespread adoption of PET, overall survival among the Medicare NSCLC population increased less than 4% between 1993 and 2005. Using regression analyses, we found that previous optimistic assessments of the survival benefit of PET may be attributed in part to selection bias. That is, PET use was associated with decreased likelihood of stage IV metastatic disease, suggesting that receipt of PET is more common among patients with less advanced disease. Because PET is a more sensitive modality for detecting extent of disease, we expected its use to be associated with more advanced disease. We found that PET was preferentially administered to patients with early stage disease. This is likely due to the appropriate use of PET in evaluating primarily localized disease for evidence of occult metastases, avoiding of PET use in frank metastatic disease, preferential use of PET in patients with improved health care access, or a combination of all three. The 2003 American Society of Clinical Oncologists (ASCO) guidelines recommend that PET be reserved for patients in whom metastatic disease was not evident, instead using it to rule out occult metastatic disease prior to invasive lung surgery.[31] Our findings may explain results from a previous report which concluded that PET use conferred a roughly two fold increase in survival[4]. Had gains in survival of this magnitude been caused by PET, overall improvement in NSCLC survival should have increased by 30% following uptake of PET by over half of the Medicare NSCLC population.

In addition to selection bias, we also found that the proportion of patients staged as having incurable disease increased from 40% to 50% between 1998 and 2005. In addition, we found that stage-specific survival improved dramatically among patients with advanced disease,

with the likelihood of being alive two-years after a diagnosis of incurable disease increasing from 10% to 16% between 1998 and 2005. These findings provided evidence of PET-induced stage migration between 1998 and 2005 that resulted in stage-specific improved survival in the without similar changes in overall survival.[32,33] The clinical value of PET may evolve with emerging molecularly-targeted therapies, which were not in use during the time frame analyzed by this study. The artificial improvement in stage-specific survival is important, since trials of new therapies often rely on historical controls to evaluate the effect on patient survival. If historical patient cohorts are used in this manner without consideration of PET use and stage migration, new treatments could falsely claim a survival benefit in advanced stage disease.

8.3 Study 3: The Effect of PET on patient treatment and health care costs

Another potential benefit of PET is the avoidance of futile thoracotomy, which occurs when a patient with metastatic disease undergoes local, definitive treatment for an incurable disease. One small randomized trial[34] has suggested that the use of PET may result in appropriate upstaging, reduce futile thoracotomy, and save costs, although it is unknown whether or not this can be extrapolated to the general Medicare NSCLC population. In privately-insured patient populations, PET has been associated with upstaging of NSCLC [33] that would also suggest a potential towards avoiding futile thoracotomy and associated inpatient hospitalization. In our second study, we found evidence of PET-induced stage-migration among Medicare NSCLC patients. Prior to this study, however, the potential of PET to reduce futile local control and decrease inpatient costs had not been examined within the Medicare NSCLC population.

After controlling for shifting demographics, we found that Medicare NSCLC rates of surgery decreased between 1998 and 2005, supporting the possibility that PET-induced stage migration reduced rates of futile thoracotomy and could potentially have resulted in subsequent inpatient health care savings. Estimates from 2003-2005 suggest a reduction of 11% in inpatient expenditures, which in 2005 would have amounted to $2,800 in inpatient savings per patient. After accounting for the average cost of a PET scan during the same period ($1,400) suggests that the introduction of PET into the Medicare NSCLC may have saved roughly $1,400 per diagnosis.

Previous studies support a similar concept. A randomized trial of PET use in 337 early stage NSCLC patients found that PET-CT correctly upstaged an additional 7% of patients and reduced futile thoracotomy and overall costs compared with conventional CT-based staging [34]. Assuming a similar effect size in our study and a historic rate of early stage disease of roughly 60% would predict a decrease in overall surgical resection of approximately 4%, comparable to 3.4% reduction we observed between the 1998-1999 and 2004-2005 cohorts.

An unexpected finding, however, was that during the same period, the use of chemotherapy and non-inpatient expenditures increased rapidly, offsetting potential savings in inpatient expenditures. Despite stable or decreasing inpatient costs, overall health care costs increased by an average of $10,200 per patient between 1993-1994 and 2004-2005. We previously reported an average increase in overall imaging costs of $1,500 per patient between 1999 and 2004 [3], which would leave an unexplained increase in overall costs of $8,500. Increased costs between 1993 and 2005 coincided with a substantial increase in the proportion of patients undergoing chemotherapy and the proportion of patients with multiple comorbidities, both of which were associated with substantial increases in total health care costs. One

interpretation of these findings are that PET reduces health care costs by reducing rates of futile thoracotomy, but increases costs by now referring these patients for systemic chemotherapy reserved for incurable disease. Our results suggest that changing patient demographics and the increase use of chemotherapy are in part responsible for the observed actual increase in Medicare spending.

8.4 Limitations

This study has several limitations as a retrospective, claims-based analysis. First, only PET scans paid for by Medicare could be detected in our analysis. However, it is likely that relatively few PET scans for our sample of Medicare beneficiaries would be paid by third party insurers or out of pocket. Second, it is unknown how reliable Medicare claims data are for determining receipt of PET. However, studies examining the accuracy of Medicare claims for assessing alternative imaging modalities such as mammography have had observed concordance rates of 94% [35]. Third, patients within the SEER registry are overall more likely to be non-white, live in non-poverty areas, and live in urban areas[36], which may limit the ability to generalize our findings. Fourth, we did not incorporate patient stage, treatment decisions, survival, or other factors that could themselves altered by receipt of PET. Fifth, our analysis of distance between patient residence and PET providing facilities was based on distances between zip code centroids as a surrogate for travel time [37]. Finally, SEER-Medicare data are released with a several year lag, limiting the ability of the analysis to extend beyond 2005 at the time of the study.

Collection of cancer T, N, and M information used to extract cancer stage changed in 1998 and again in 2004.[38] Prior to 1998, information used to stage cancers was obtained using all available information in the two months following diagnosis. Beginning in 1998 onward, this timeframe was extended to four months or first surgery. This likely resulted in a slight increase

in advanced stage disease between 1997 and 1998. In 2004, data collection within SEER changed from the extend of disease (EOD) collection system to the collaborative staging system (CSS). It is unclear how this should have affected staging. These complicated changes in staging were fortunately accompanied by an opportunistic window between 1998 and 2003, during which no known artifacts in staging occurred, but the largest changes in PET utilization and stage migration were observed.

On a more general level, studies 2 and 3 were both extremely limited by the bidirectional, causal link between receipt of PET and disease stage. The selective administration of PET to patients with early stage disease made direct inference of the effect of PET on NSCLC stage, survival, costs, and treatment challenging. The inability to draw reliable inference from conventional epidemiology methodologies in this setting provided a significant challenge to my research and its conclusions. In the end, simple plots of overall survival, stage distribution, treatment, and costs provided significant support for our theories.

There are several potential factors other than the introduction of PET that may have affected patient outcomes between 1998 and 2005. In 2003, ASCO recommendations were expanded to include the use of dual vs. single chemotherapy agents in the treatment of NSCLC. Recently, a randomized trial of early palliative care found a survival benefit comparable to chemotherapy. [39] The incorporation of new chemotherapy, molecularly targeted drugs, palliative care, or alternative interventions that could have affected survival over the study period make it difficult to interpret temporal changes over time.

8.5 Future Research

Many questions remain regarding the use of advanced imaging modalities in oncology and a large number of potential research directions stem from the current work. Potential avenues of research range from further imaging studies in NSCLC, examination of advanced imaging modalities in other cancer sites such as prostate cancer or lymphoma, methodologic work to model how imaging enters clinical decision making and outcomes, cost-effectiveness research of advanced imaging use in cancer, or any of the above in combination with newly emerging treatment options. All of these potential projects may be additionally assisted by availability of Medicare Part D prescription drug data, which recently became available beginning with patient data from 2006 onward. Two examples of oral chemotherapy agents used in the treatment of lung cancer include etoposide and tarceva, which were not observed in this study but are often administered in the palliative setting.[31,40] Because of a largely palliative role of these agents, their use may be specifically increased by PET-induced stage migration. Future studies to examine more specifically how PET affects patient management and chemotherapy selection could make a significant impact on how we allot health care dollars in these settings. Modeling these complex interactions between imaging and cancer management may be useful to develop effective cost-conserving policies in an era of rapidly increasing health care costs. Recently, a randomized trial of early palliative care found a survival benefit comparable to chemotherapy, [39] highlighting the potential for other factors besides chemotherapy to have affected patient survival and could be investigated.

Continuing evaluation of the effect of PET on overall cancer patient evaluation, management, and outcomes will likely be aided in the future by the continued implementation of national, prospective databases of PET use such the National Oncologic PET Registry (NOPR).[41-43] However, because the use of PET in NSCLC has long been approved by Medicare,

it is unlikely that the NOPR registry will provide coverage with evidence development (CED) for a significant portion of NSCLC PET scans.

8.6 Conclusion

Fully understanding the utilization of PET and how it affects staging, management, outcomes, and health care spending in lung cancer patients has considerable implications for establishing future imaging guidelines. Prior to the studies performed in this dissertation, previous analyses have suggested an association between PET and improved NSCLC patient survival [4, 4,33,44]. Our finding suggest that these studies may not have fully adjusted for PET selection bias and PET-induced stage-migration, both of which may exaggerate the beneficial effect of PET on patient survival. Because there is unlikely to be a large randomized controlled trial to definitively assess the overall effect of PET on patient outcomes, researchers must carefully characterize and control for PET selection bias and stage-migration when performing non-experimental evaluations of PET. When we did so, we concluded that PET does not confer a survival benefit in NSCLC. However, we provide evidence that PET may be able to reduce futile thoractomies and potentially save health care dollars. This research marks the first effort to fully assess both the direct and indirect costs and benefits of PET use in the Medicare NSCLC population and helps to inform future Medicare policy decisions regarding the use of PET.

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